Annex III

Product information

Note:

This product information is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection
{(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection]
1 ml of solution for injection contains 40 mg of articaine hydrochloride and 5 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml of solution for injection contains 68 mg of articaine hydrochloride and 8.5 micrograms of adrenaline (as adrenaline tartrate).

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection]
1 ml of solution for injection contains 40 mg of articaine hydrochloride and 10 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml of solution for injection contains 68 mg of articaine hydrochloride and 17 micrograms of adrenaline (as adrenaline tartrate).

Excipients with known effect: sodium metabisulfite (E223), sodium chloride, disodium edetate, sodium hydroxide.
{(Invented) name and associated names (see Annex I)} contains 0.804 mg sodium per 1 ml of solution i.e. 1.44 mg/1.7 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local and loco-regional anaesthesia in dental procedures.
{(Invented) name and associated names (see Annex I)} is indicated in adults, adolescents and children above 4 years of age (or from 20 kg (44 lbs) of body weight).

4.2 Posology and method of administration

For professional use by physicians or dentists only.

Posology

For all populations, the lowest dose leading to effective anaesthesia should be used. The necessary dosage must be determined on an individual basis.

For a routine procedure, the normal dose for adult patients is of 1 cartridge, but the contents of less of a cartridge may be sufficient for effective anaesthesia. At the discretion of the dentist, more cartridges may be required for more extensive procedures without exceeding the maximum recommended dose.

For most routine dental procedures, it is preferable to use {(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml.
For more complex procedures, such as requiring pronounced hemostasis, it is preferable to use {(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml.

Concomitant use of sedatives to reduce patient anxiety:
The maximum safe dose of local anaesthetics may be reduced in sedated patients due to an additive effect on central nervous system depression (see section 4.5).

● Adults and adolescents (12 to 18 years of age)
In adults and adolescents, the maximum articaine dose is 7 mg/kg with an absolute maximum articaine dose of 500 mg. The maximum articaine dose of 500 mg corresponds to a healthy adult of more than 70 kg body weight.
The table below illustrates the maximum recommended dose:

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection]

Patient body weight (kg)	**Maximum dose of articaine hydrochloride (mg)**	**Dose of adrenaline (mg)**	**Total volume (ml) and equivalent in number of cartridges (1.7 ml)**
40	280	0.035	7.0 (4.1 cartridges)
50	350	0.044	8.8 (5.2 cartridges)
60	420	0.053	10.5 (6.2 cartridges)
70 or more	490	0.061	12.3 (7.0 cartridges)

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection]

Patient body weight (kg)	**Maximum dose of articaine hydrochloride (mg)**	**Dose of adrenaline (mg)**	**Total volume (ml) and equivalent in number of cartridges (1.7 ml)**
40	280	0.070	7.0 (4.1 cartridges)
50	350	0.088	8.8 (5.2 cartridges)
60	420	0.105	10.5 (6.2 cartridges)
70 or more	490	0.123	12.3 (7.0 cartridges)

● Children (4 to 11 years of age)
The safety of {(Invented) name and associated names (see Annex I)} in children aged 4 years and below has not been established. No data are available.
The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average effective dose of articaine is 2 mg/kg and 4 mg/kg for simple and complex procedures, respectively. The lowest dose providing effective dental anaesthesia should be used. In children aged 4 years (or from 20 kg (44 lbs) of body weight) and above, the maximum dose of articaine is 7 mg/kg only with an absolute maximum dose of 385 mg articaine for a healthy child of 55 kg body weight.
The table below illustrates the maximum recommended dose:

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection]

Patient body weight (kg)	**Maximum dose of articaine hydrochloride (mg)**	**Dose of adrenaline (mg)**	**Total volume (ml) and equivalent in number of cartridges (1.7 ml)**
20	140	0.018	3.5 (2.1 cartridges)
30	210	0.026	5.3 (3.1 cartridges)
40	280	0.035	7.0 (4.1 cartridges)
55	385	0.048	9.6 (5.6 cartridges)

[(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection]

Patient body weight (kg)	**Maximum dose of articaine hydrochloride (mg)**	**Dose of adrenaline (mg)**	**Total volume (ml) and equivalent in number of cartridges (1.7 ml)**
20	140	0.035	3.5 (2.1 cartridges)
30	210	0.053	5.3 (3.1 cartridges)
40	280	0.070	7.0 (4.1 cartridges)
55	385	0.096	9.6 (5.6 cartridges)

● Special populations

Elderly and Patients with renal disorders:
Due to the lack of clinical data, particular precaution should be used in order to administer the lowest dose leading to effective anaesthesia in elderly patients and in patients with renal disorders (section 4.4 and 5.2).
Elevated product plasma levels may occur in these patients in particular after repeated use. In case of required reinjection, patient should be strictly monitored, to identity any sign of relative overdose (see section 4.9).

Patients with hepatic impairment
Particular precaution should be used in order to administer the lowest dose leading to efficient anaesthesia in patients with hepatic impairment, in particular after repeated use, although 90% of articaine is first inactivated by unspecific plasma esterases in the tissue and blood.

Patients with plasma cholinesterase deficiency
Elevated product plasma levels may occur in patients with cholinesterase deficiency or under acetylcholinesterase inhibitors treatment since the product is inactivated at 90% by plasmatic esterases, see section 4.4 and 5.2. Therefore, the lowest dose leading to effective anaesthesia should be used.

Method of Administration

Infiltration and perineural use in oral cavity.

Local anaesthetics should be injected with caution when there is inflammation and/or infection at the site of the injection. The rate of injection should be very slow (1 ml/min).

Precautions to be taken before handling or administering the medicinal product

This medicinal product should only be used by or under the supervision of physicians or dentists sufficiently trained and familiar with diagnosis and treatment of systemic toxicity. The availability of appropriate resuscitation equipment and medication should be ensured before induction of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies. The patient's state of consciousness should be monitored after each local anaesthetic injection.

When using {(Invented) name and associated names (see Annex I)} for infiltration or regional block anaesthesia, injection should always be made slowly and with prior aspiration.

For instructions on the handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to articaine (or any local anaesthetic agent of the amide type), to adrenaline or to any of the excipients listed in section 6.1.
- Patients with epilepsy not controlled by treatment.

4.4 Special warnings and precautions for use

Before using this medicinal product, it is important:
- To make inquiries into the patient's current therapies and history;
- To maintain verbal contact with the patient
- To have resuscitative equipment at hand (see section 4.9)

Special warnings

This medicinal product must be used with special caution in patients with the following disorders and postponement of dental surgery should be considered if the condition is severe and/or unstable.

Patients with cardiovascular disorders:
The lowest dose leading to efficient anaesthesia should be used in case of:
- Cardiac impulse formation and conduction disturbances (e.g. 2nd or 3rd degree atrioventricular block, marked bradycardia)
- Acute decompensated heart failure (acute congestive heart failure)
- Hypotension
- Patients with paroxysmal tachycardia or absolute arrhythmias with rapid heart rate
- Patients with unstable angina or a history of recent (less than 6 months) myocardial infarction
- Patients with recent (3 months) coronary artery bypass surgery

- Patients taking non-cardioselective beta-blockers (e.g. propranolol) (risk of hypertensive crisis or severe bradycardia), (see section 4.5)
- Patients with uncontrolled hypertension
- Concomitant treatment with tricyclic antidepressants, as these active substances can intensify the cardiovascular effects of adrenaline. (see section 4.5)

This medicinal product must be used with caution in patients with the following disorders:

Patients with epileptic disease:
Because of their convulsive actions, all local anaesthetics should be used very cautiously.

Patients with plasma cholinesterase deficiency
A plasma cholinesterase deficiency can be suspected when clinical signs of overdose occurs with usual dosage of anesthesia and when a vascular injection has been excluded. In this case, caution shall be used for the next injection and reduced dose shall be applied.

Patients with renal disease:
The lowest dose leading to effective anaesthesia should be used.

Patients with severe hepatic disease:
This medicinal product should be used cautiously due to the presence of hepatic disease although 90% of articaine is first inactivated by unspecific plasma esterases in the tissue and blood.

Patients with myasthenia gravis treated by acetylcholinesterase inhibitors:
The lowest dose leading to effective anaesthesia should be used.

Patients with porphyria
{(Invented) name and associated names (see Annex I)} should only be used in patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in all patients with porphyria, as this medicinal product can trigger porphyria.

Patients with concomitant treatment with halogenated inhalation anaesthetics
The lowest dose of the medicinal product leading to effective anaesthesia should be used (see section 4.5).

Patients receiving treatment with antiplatelets / anticoagulants:
{(Invented) name and associated names (see Annex I)} should be administered with caution in patients, who are using antiplatelet/anticoagulant medicines or are suffering from coagulation disorder, because of higher risk of bleeding. The higher risk of bleeding is more associated with the procedure, rather than with the medicine.

Elderly patients:
Elevated product plasma levels may occur in elderly patients in particular after repeated use. In case of required reinjection, patient should be strictly monitored, to identity any sign of relative overdose (see section 4.9).
Therefore, the lowest dose leading to effective anaesthesia should be used.

The use of {(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection over {(Invented) name and associated names (see Annex I)} 40 mg/ ml + 10 micrograms/ml, solution for injection should be considered on account of its lower adrenaline content of 5 micrograms/ml in:

- *Patients with cardiovascular diseases* (e.g. heart failure, coronary heart disease, history of myocardial infarction, cardiac arrhythmia, hypertension)

- *Patients with cerebral circulation disturbances, history of strokes*

It is recommended that dental treatment with articaine/adrenaline be deferred for six months following a stroke due to the increased risk of recurrent strokes.

- *Patients with uncontrolled diabetes:*
  This medicinal product should be used cautiously due to hyperglycemic effect of adrenaline.

- *Patients with thyreotoxicosis:*
  This medicinal product should be used cautiously due to the presence of adrenaline.

- *Patients with pheochromocytoma:*
  This medicinal product should be used cautiously due to the presence of adrenaline.

- *Patients with susceptibility of acute angle-closure glaucoma:*
  This medicinal product should be used cautiously due to the presence of adrenaline.

The lowest dose leading to effective anaesthesia should be used.

This medicinal product must be used safely and effectively under appropriate conditions:
Adrenaline impairs the flow of blood in the gums, potentially causing local tissue necrosis.
Very rare cases of prolonged or irreversible nerve injury and gustatory loss have been reported after mandibular block analgesia.

The local anaesthetic effects may be reduced when this medicinal product is injected into an inflamed or infected area.

The dose must also be reduced in case of hypoxia, hyperkalaemia and metabolic acidosis.

Risk of biting trauma (lips, cheeks, mucosa, and tongue) exists, especially in children; the patient should be told to avoid chewing gum or eating until normal sensation is restored.

This medicinal product contains sodium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.
This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge, i.e. it is considered as essentially “sodium free”.

If there is any risk of an allergic reaction, choose a different medicine for anesthesia (see section 4.3).

Precautions for use

Risk associated with accidental intravascular injection:

Accidental intravascular injection may cause sudden high levels of adrenaline and articaine in the systemic circulation. This may be associated with severe adverse reactions, such as convulsions, followed by central nervous and cardiorespiratory depression and coma, progressing to respiratory and circulatory arrest.
Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the local anaesthetic medicinal product is injected. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Risk associated with intraneural injection:

Accidental intraneural injection may lead the drug to move in retrograde manner along the nerve.
In order to avoid intraneural injection and to prevent nerve injuries in connection with nerve blockades, the needle should always be slightly withdrawn if electric shock sensation is felt by the patient during injection or if the injection is particularly painful. If needle nerve injuries occur, the neurotoxic effect could be aggravated by articaine potential chemical neurotoxicity and the presence of adrenaline as it may impair the perineural blood supply and prevent articaine local wash-out.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with articaine

***Interactions requiring precautions for use*:**

Other local anaesthetics
Toxicity of local anaesthetics is additive.
The total dose of all local anaesthetics administered should not exceed the maximum recommended dose of the drugs used.

Sedatives (central nervous system depressants e.g. benzodiazepine, opioids):
If sedatives are employed to reduce patient's apprehension, reduced doses of anaesthetics should be used since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect (see section 4.2).

Interactions with adrenaline

Interactions requiring precautions for use:

Halogenated volatile anaesthetics (e.g., halothane):
Reduced doses of this medicinal product should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia.
Discussion with the anaesthetist before local anaesthetic administration during general anaesthesia is recommended.

Postganglionic adrenergic blocking agents (e.g., guanadrel, guanethidine, and rauwolfia alkaloids):
Reduced doses of this medicinal product should be used under strict medical supervision with careful aspiration due to possible increase response to adrenergic vasoconstrictors: risk of hypertension and other cardiovascular effects.

Non-selective beta-adrenergic blockers (e.g., propranolol, nadolol):
Reduced doses of this medicinal product should be used due to possible increase in blood pressure and an increased risk of bradycardia.

(TCAs) Tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline):
Dose and rate of administration of this medicinal product should be reduced due to an increased risk of severe hypertension.

COMT inhibitors (Catechol-O-methyl transferase inhibitors) (e.g., entacapone, tolcapone):
Arrhythmias, increased heart rate and blood pressure variations may occur.
A reduced amount of adrenaline in dental anaesthesia should be given to patients on COMT inhibitors.

MAO inhibitors (both A-selective (e.g. moclobemide) and non-selective (e.g. phenelzine, tranylcypromine, linezolide) :
If the concurrent use of these agents cannot be avoided, the dose and rate of administration of this product should be reduced, and the product should be used under strict medical supervision due to possible potentiation of the effects of adrenaline leading to the risk of hypertensive crisis."

Drugs causing arrhythmias (e.g., antiarrhythmics like digitalis, quinidine):
Dose of administration of this medicinal product should be reduced due to the increased risk of arrhythmia when both adrenaline and digital glucosides are administered concomitantly to patients. Careful aspiration prior to administration is recommended.

Ergot-type oxytocic drugs (e.g., methysergide, ergotamine, ergonovine):
Use this medicinal product under strict medical supervision due to additive or synergistic increases in blood pressure and/or ischemic response.

Sympathomimetic vasopressors (e.g., mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline):
There is a risk of adrenergic toxicity.
If any sympathomimetic vasopressor has been used within 24 hours, the planned dental treatment should be postponed.

Phenothiazines (and other neuroleptics):
Use with caution in patients taking phenothiazines considering the risk of hypotension due to possible inhibition of adrenaline effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with articaine 40 mg/ml + adrenaline 10 micrograms/ml, as well as with articaine alone, have not shown adverse effects on pregnancy, embryonal/foetal development, birth or postnatal development (see section 5.3).
Animal studies have shown that adrenaline is toxic to reproduction at doses higher than maximal recommended dose (see section 5.3).
There is no experience of the use of articaine in pregnant women, except during childbirth. Adrenaline and articaine cross the placental barrier, although articaine does so to a lesser extent than other local anaesthetics. Serum concentrations of articaine measured in newborn infants were approx. 30% of maternal levels. In the event of inadvertent intravascular administration in the mother, adrenaline can reduce uterine perfusion.

During pregnancy, {(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml should only be used after a careful analysis of the benefit-to-risk ratio has been made.

On account of its lower adrenaline content, the use of {(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection over {(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection should be preferred.

Breastfeeding

As a result of the rapid drop in serum levels and rapid elimination, clinically relevant quantities of articaine are not found in breast milk. Adrenaline passes into breast milk but also has a short half-life.
It is not usually necessary to suspend breast-feeding for short-term use, starting from 5 hours following anesthesia.

Fertility

Animal studies with articaine 40 mg/ml + adrenaline 10 micrograms/ml have not shown effects on fertility (see section 5.3). At therapeutic doses, adverse effects on human fertility are not expected.

4.7 Effects on ability to drive and use machines

The combination articaine hydrochloride with adrenaline tartrate solution for injection may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of {(Invented) name and associated names (see Annex I)} (see Section 4.8 of SmPC). So, patients should not leave the dental office until they recover their abilities (generally within 30 minutes) following the dental procedure.

4.8 Undesirable effects

a) Summary of the safety profile

Adverse reactions following administration of articaine / adrenaline are similar to those observed with other local amide anaesthetics / vasoconstrictors. These adverse reactions are, in general, dose-related. They may also result from hypersensitivity, idiosyncrasy, or diminished tolerance by patient. Nervous system disorders, local injection site reaction, hypersensitivity, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.
Serious adverse reactions are generally systemic.

b) Tabulated list of adverse reactions

The reported adverse reactions come from spontaneous reporting, clinical studies and literature**.**
The frequencies classification follows the convention: 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), and very rare (<1/10,000)
Not known (cannot be estimated from the available data)".

MedDRA Sytem Organ Class	**Frequency**	**Adverse Reactions**
Infections and infestations	Common	Gingivitis
Immune system disorders	Rare	Allergic[1], anaphylactic / anaphylactoid reactions
Psychiatric disorders	Rare	Nervousness / anxiety[4]
	Not known	Euphoric mood
Nervous system disorders	Common	Neuropathy: Neuralgia (neuropathic pain) Hypoesthesia / numbness (oral and perioral) [4] Hyperesthesia Dysesthesia (oral and perioral), *including* Dysgeusia (e.g., taste metallic, taste disturbance) Ageusia Allodynia Thermohyperesthesia Headache
	Uncommon	Burning sensation
	Rare	Facial nerve disorder[2] (palsy,

		paralysis and paresis) Horner's syndrome (eyelid ptosis, enophthalmos, miosis). Somnolence (Drowsiness) Nystagmus
	Very rare	Paresthesia[3] (persistent hypoesthesia and gustatory loss) after mandibular or inferior alveolar nerve blocks
Eye disorders	Rare	Diplopia (paralysis of oculomotor muscles)[4] Visual impairment (temporary blindness)[4] Ptosis Miosis Enophthalmos
Ear and labyrinth disorders	Rare	Hyperacusis Tinnitus[4]
Cardiac disorders	Common	Bradycardia Tachycardia
	Rare	Palpitations
	Not known	Conduction disorders (atrioventricular block)
Vascular disorders	Common	Hypotension (with possible circulatory collapse)
	Uncommon	Hypertension
	Rare	Hot flush
	Not known	Local / Regional hyperaemia Vasodilatation Vasoconstriction
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm / asthma Dyspnoea[2]
	Not known	Dysphonia (Hoarseness)[1]
Gastrointestinal disorders	Common	Swelling of tongue, lip, gums
	Uncommon	Stomatitis, glossitis Nausea, vomiting, diarrhoea
	Rare	Gingival / oral mucosal exfoliation (sloughing) / ulceration
	Not known	Dysphagia Swelling of cheeks Glossodynia
Skin and subcutaneous tissue disorders	Uncommon	Rash (eruption) Pruritus
	Rare	Angioedema (face / tongue / lip / throat / larynx / periorbital oedema) Urticaria
	Not known	Erythema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Neck pain
	Rare	Muscle twitching[4]
	Not known	Aggravation of the neuromuscular manifestations in Kearns-Sayre

		syndrome Trismus
General disorders and administration site conditions	Uncommon	Injection site pain
	Rare	Injection site exfoliation / necrosis Fatigue, asthenia (weakness)/ Chills
	Not known	Local swelling Feeling hot, Feeling cold

c) Description of selected adverse reactions

[1] Allergic reactions should not be mistaken with syncopal episodes (cardiac palpitations due to adrenaline).

[2] A 2 week delay in the onset of facial paralysis has been described following administration of articaine combined with adrenaline, and the condition was unchanged 6 months later.

[3] These neural pathologies may occur with various symptoms of abnormal sensations. Paresthesia can be defined as spontaneous abnormal usually non-painful sensation (e.g., burning, pricking, tingling or itching) well beyond the expected duration of anesthesia. Most cases of paresthesia reported following dental treatment are transient and resolve within days, weeks or months.
Persistent paresthesia, mostly following nerve blocks in the mandible, is characterized by slow, incomplete, or lack of recovery.

[4] Several adverse events, like agitation, anxiety / nervousness, tremor, speech disorder may be warning signs before CNS depression. In attendance of these signs, patients should be requested to hyperventilate and surveillance should be instituted (see Section 4.9 of SmPC).

d) Paediatric population

The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults. However, accidental soft tissue injury was observed more frequently, especially in 3 to 7 year old children, due to the prolonged soft tissue anaesthesia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system listed in Appendix V.

4.9 Overdose

Types of overdose

Local anaesthetic overdose in the largest sense is often used to describe:

- absolute overdose,
- relative overdose such as:
  - inadvertent injection into a blood vessel, or
  - abnormal rapid absorption into the systemic circulation, or
  - delayed metabolism and elimination of drug.

In case of relative overdose, patients generally present symptoms within the first minutes. Whereas in case of absolute overdose, signs of toxicity, depending on the injection site, appear later after the injection.

Symptoms

Due to an overdose (absolute or relative), since excitement may be transient or absent, the first manifestations may be drowsiness merging into unconsciousness and respiratory arrest.

Due to articaine:
The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations (presyncope, syncope, headache, restlessness, agitation, confusional state, disorientation, dizziness (lightheadedness), tremor, stupor, deep CNS depression, loss of consciousness, coma, convulsion (including tonic-clonic seizure), speech disorder (e.g., dysarthria, logorrhea), vertigo, balance disorder (disequilibrium)), eyes manifestations (mydriasis, vision blurred, accommodation disorder) followed by vascular (pallor (local, regional, general)), respiratory (apnoea (respiratory arrest), bradypnoea, tachypnoea, yawning, respiratory depression) and finally cardiac (cardiac arrest, myocardial depression) toxicity.
Acidosis exacerbates the toxic effects of local anaesthetics.

Due to adrenaline:
The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations (restlessness, agitation, presyncope, syncope) followed by vascular (pallor (local, regional, general)), respiratory (apnoea (respiratory arrest), bradypnoea, tachypnoea, respiratory depression) and finally cardiac (cardiac arrest, myocardial depression) toxicity.

Treatment of overdose

The availability of resuscitation equipment and medication should be ensured before administration of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies.
The seriousness of overdose symptoms should have physicians/dentists to implement protocols that foresee the necessity of timely securing the airway and providing assisted ventilation.
The patient's state of consciousness should be monitored after each local anaesthetic injection.
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately. Change patient position to supine position if necessary.
CNS symptoms (convulsions, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.
Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis may prevent cardiac arrest.
If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and/or inotropic agents should be considered. Children should be given doses commensurate with age and weight.
In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation should be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous System / Local Anaesthetics / Anaesthetics, local / Amides / Articaine, combinations
ATC code: N01BB58

Mechanism of action and pharmacodynamic effects:
Articaine, a local amide anaesthetic, reversibly blocks nerve conduction through a well-known mechanism commonly observed with other local amide anaesthetics. This consists in decreasing or preventing the large transient increase in the permeability of excitable membranes to sodium (Na^+) that is normally produced by slight depolarisation of the membrane. These actions lead the anaesthetic action. As the anaesthetic action progressively develops in the nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines and impulse conduction slows. The pKa of articaine has been estimated at 7.8.

Adrenaline, as vasoconstrictor, acts directly on both α- and β-adrenergic receptors; β-adrenergic effects predominate. Adrenaline prolongs the effect duration of the articaine, and reduces the risk of excessive uptake of articaine into the systemic circulation.

Clinical efficacy and safety: {(Invented) name and associated names (see Annex I)} has an onset of 1.5-1.8 min for infiltration and 1.4-3.6 min for nerve block.
The anaesthetic duration of articaine 40 mg/mL with adrenaline 1: 100 000 is of 60 to 75 minutes for pulpal anaesthesia and 180 to 360 minutes for soft tissue anaesthesia.
The anaesthetic duration of articaine 40 mg/mL with adrenaline 1: 200 000 is of 45 to 60 minutes for pulpal anaesthesia and 120 to 300 minutes for soft tissue anaesthesia.

No difference was observed in pharmacodynamic properties between the adult and the paediatric population.

5.2 Pharmacokinetic properties

- ***Articaine***

Absorption: In three published clinical studies describing the pharmacokinetic profile of the combination articaine hydrochloride 40 mg/ml with adrenaline 10 or 5 micrograms/ml, T_{max} values were between 10 and 12 minutes, with C_{max} values ranging from 400 to 2100 ng/ml.
In clinical trials performed in children, C_{max} was 1382 ng/ml and T_{max} 7.78 min following infiltration of a dose of 2 mg/kg body weight.

Distribution: High protein binding of articaine was observed with human serum albumin (68.5-80.8%), and ∝/β-globulins (62.5-73.4%). Binding to γ-globulin (8.6-23.7%) was much lower. Adrenaline is a vasoconstrictor added to articaine to slow down absorption into the systemic circulation and thus prolong maintenance of active articaine tissue concentration.The volume of distribution in plasma was about 4 l/kg.

Biotransformation: Articaine is subject to hydrolysis of its carboxyl group by unspecific esterases in the tissue and in blood. Since this hydrolysis is very fast, about 90% of articaine is inactivated by this way. Articaine is additionally metabolised in the liver microsomes. Articainic acid is the major product of cytochrome P450-induced metabolism of articaine, further metabolised to form articainic acid glucuronide.

Elimination: Following dental injection, the elimination half-life of articaine was c.a. 20-40 min. In a clinical trial, plasma concentrations of articaine and articainic acid were shown to decrease rapidly following submucosal injection. Very little articaine was detected in plasma from 12 to 24 hours following injection. More than 50% of the dose was eliminated in the urine, 95% as articainic acid, within 8 hours of administration. Within 24 hours, approximately 57% (68 mg) and 53% (204 mg) of the dose was eliminated in the urine. Renal elimination of unchanged articaine accounted for only about 2% of total elimination.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans at therapeutic doses, based on conventional studies of safety pharmacology, chronic toxicity, reproductive toxicity and genotoxicity.

At supratherapeutic doses, articaine has cardiodepressant properties and can exert vasodilatory effects. Adrenaline exhibits sympathomimetic effects.
Subcutaneous injections of articaine combined with adrenaline induced adverse effects from 50 mg/kg/day in rats and 80 mg/kg/day in dogs after 4 weeks daily repeated administrations. However, these findings are of little relevance to its clinical use as acute administration.

In embryotoxicity studies with articaine, no increase in the foetal mortality rate or malformations were observed at daily i.v. doses of up to 20 mg/kg in rats and 12.5 mg/kg in rabbits.
Teratogenecity was observed in animals treated with adrenaline only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Reproductive toxicity studies conducted with articaine 40 mg/ml + adrenaline 10 micrograms/ml administered by the subcutaneous route at doses up to 80 mg/kg/day revealed no adverse effects on fertility, embryonal/foetal development, or pre- and postnatal development.

No genotoxicity effect was observed during in-vitro and in-vivo studies conducted with articaine alone or in an in vivo study conducted with articaine in combination with adrenaline.
Contradictory findings were raised from in-vitro and in-vivo genotoxicity studies with adrenaline.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium edetate
Sodium metabisulfite (E223)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
Keep the cartridges in the tightly closed outer carton in order to protect from light .

6.5 Nature and content of container

Single use cylindrical class I glass cartridge sealed at its base by a mobile rubber plunger and at the top by a rubber seal kept in place by an aluminium cap.

Box containing glass cartridges 50 x 1.7 ml.
Box containing glass cartridges, self-aspirating 50 x 1.7 ml.
Pack of 4 boxes containing glass cartridges 50 x 1.7 ml.
Pack of 8 boxes containing glass cartridges 50 x 1.7 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

To avoid risk of infection (e.g. hepatitis transmission), syringe and needles used to draw up the solution must always be fresh and sterile.

This medicinal product should not be used if the solution is cloudy or discoloured.

The cartridges are intended for single use. If only a portion of a cartridge is used, the remainder must be discarded.
Use immediately after the opening of the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8 MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection

articaine hydrochloride/adrenaline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for injection contains 40 mg of articaine hydrochloride and 5 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml contains 68 mg of articaine hydrochloride and 8.5 micrograms of adrenaline (as adrenaline tartrate).

3. LIST OF EXCIPIENTS

Sodium chloride, disodium edetate, sodium metabisulfite (E223), sodium hydroxide, water for injections.
Contains sodium and metabisulfite, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

50 x 1.7 ml cartridges
50 x 1.7 ml cartridges, selfaspirating
4 (50 x 1.7 ml) cartridges
8 (50 x 1.7 ml) cartridges

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Infiltration and perineural use.
Dental use.
Read the package leaflet before use.
For single use
Use immediately after the opening of the cartridge

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.
Keep the cartridges in the tightly closed outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only.
Discard unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
<NN: {number} >

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label (cartridge)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection
articaine hydrochloride/adrenaline

Dental use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.7 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection

articaine hydrochloride/adrenaline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for injection contains 40 mg of articaine hydrochloride and 10 micrograms of adrenaline (as adrenaline tartrate).
Each cartridge of 1.7 ml contains 68 mg of articaine hydrochloride and 17 micrograms of adrenaline (as adrenaline tartrate).

3. LIST OF EXCIPIENTS

Sodium chloride, disodium edetate, sodium metabisulfite (E223), sodium hydroxide, water for injections.
Contains sodium and metabisulfite, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

50 x 1.7 ml cartridges
50 x 1.7 ml cartridges, selfaspirating
4 (50 x 1.7 ml) cartridges
8 (50 x 1.7 ml) cartridges

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Infiltration and perineural use.
Dental use.
Read the package leaflet before use.
For single use.
Use immediately after the opening of the cartridge.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.
Keep the cartridges in the tightly closed outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only.
Discard unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
<NN: {number} >

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label (cartridge)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection
articaine hydrochloride/adrenaline

Dental use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.7 ml

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

{(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml, solution for injection
{(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml, solution for injection
[See Annex I - To be completed nationally]

articaine hydrochloride/adrenaline

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your dentist, doctor or pharmacist.
- If you get any side effects, talk to your dentist, doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What X / Y is and what it is used for

X / Y is used to numb (anaesthetise) your oral cavity during dental procedures.
This medicine contains two active substances:
- articaine, a local anaesthetic which prevents pain, and
- adrenaline, a vasoconstrictor which narrows the blood vessels at the site of injection, and thereby prolongs the effect of articaine. It also decreases bleeding during surgery.

You will be given X or Y by a dentist.
X / Y is for children over 4 years of age (ca. 20 kg in body weight), adolescents and adults.

Depending on the kind of dental procedure performed, the dentist will choose between the two medicines:
- X is usually used for simple and short dental procedures
- Y is more adapted to procedures lasting longer or with possible significant bleeding.

2. What you need to know before you are given X / Y

Do not use X / Y if you suffer from any of the following conditions:
- allergy to articaine or adrenaline or any of the other ingredients of these medicines (listed in section 6);
- allergy to other local anaesthetics;
- epilepsy, not adequately controlled by drug treatment.

Warnings and precautions
Talk to your dentist before using X / Y if you suffer from any of the following conditions:
- severe heart rhythm disorders (e.g. second and third-degree AV block);
- acute heart failure (acute heart weakness, e.g. unexpected chest pain while resting or after myocardial infraction (e.g. heart attack));
- low blood pressure;
- abnormal rapid heartbeats;
- heart attack in the last 3 to 6 months;
- coronary artery bypass surgery in the last 3 months;
- taking some medicines for blood pressure called beta blockers, such as propranolol. There is the danger of a hypertensive crisis (very high blood pressure) or severe slowing of the pulse (see section other medicines);
- very high blood pressure;
- simultaneously taking some medicines for the treatment of depression and Parkinson's disease (tricyclic antidepressants). These medicines may intensify the effects of adrenaline.
- epilepsy;
- lacking of a natural chemical substance called cholinesterase in your blood (plasma cholinesterase deficiency);
- problems with your kidneys;
- serious problems with your liver
- a disease called *Myasthenia Gravis* causing weakness in the muscles*;*
- *Porphyria* which causes either neurological complications or skin problems*;*
- use other local anaesthetics, medicines that cause reversible loss of sensation (including volatile anaesthetics such as halothane);
- taking medications called antiplatelets or anticoagulants, to prevent narrowing or hardening of your blood vessels in the arms and legs;
- are more than 70 years old.
- have or have had any heart problem
- have uncontrolled diabetes;
- severely overfunctioning thyroid (thyrotoxicosis);
- tumour called pheochromocytoma;
- a disease called angle-closure glaucoma which affects your eyes;
- inflammation or infection in the area to be injected.
- decreased amounts of oxygen in the body's tissues (hypoxia), high blood potassium (hyperkalaemia) and metabolic disorders as a result of too much acid in the blood (metabolic acidosis).

Other medicines and X / Y
Tell your dentist if you are taking, have recently taken or might take any other medicines.
It is especially important to tell your dentist if you are taking any of the following medicines:
- other local anaesthetics, medicines that cause reversible loss of sensation (including volatile anaesthetics such as halothane);
- sedatives (such as benzodiazepine, opioids), for example to reduce your apprehension before the dental procedure;
- heart and blood pressure medicines (such as guanadrel, guanethidine, propranolol, nadolol,)
- tricyclic antidepressants used to treat depression (such as amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline);
- COMT-inhibitors to treat Parkinson's disease (such as entacapone or tolcapone);
- MAO inhibitors used to treat depressive or anxiety disorders (such as moclobemide, phenelzine, tranylcypromine, linezolide);
- medicines used to treat irregular heartbeats (for example digitalis, quinidine);
- medicines used for migraine attacks (such as methysergide or ergotamine);
- sympathomimetic vasopressors (such as cocaine, amphetamines, phenylephrine, pseudoephedrine, oxymetazoline), used to raise the blood pressure: if used within the past 24 hours, the planned dental

treatment has to be postponed.
- neuroleptic drugs (for example phenothiazines).

X / Y with food
Avoid eating, included chewing-gum, until normal sensation is restored because there is a risk that you may bite your lips, cheeks or tongue, especially in children.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your dentist or doctor for advice before using this medicine.

Your dentist or doctor will decide if you can use X / Y during pregnancy.
Breast-feeding can be resumed after 5 hours following anaesthesia.
No adverse effects on fertility are anticipated at doses used for a dental procedure.

Driving and using machines
If you experience side effects, including dizziness, blurred vision or fatigue, you should not drive or operate machinery until you recover your abilities (generally within 30 minutes following the dental procedure).

X / Y contains sodium and sodium metabisulfite.
- Sodium: less than 23 mg sodium per cartridge, meaning it is essentially "sodium free".
- Sodium metabisulfite: it may rarely cause severe allergic reactions and breathing difficulties (bronchospasm).

If there is any risk of an allergic reaction, your dentist will choose a different medicine for anesthesia.

3. How to use X / Y

Only physicians or dentists are trained to use X/Y.
Your dentist will choose between X and Y, and determine the appropriate dose taking into account your age, your weight, your general health and the dental procedure.
The lowest dose leading to effective anaesthesia should be used.
This medicine is given by a slow injection in the oral cavity.

If you are given more X / Y than you should
It is not likely that you will be given too much of this injection but if you should begin to feel unwell, tell your dentist. Symptoms of overdose include severe weakness, paleness of the skin, headache, feeling agitated or restless, feeling disorientated, losing your balance, involuntary trembling or quivering, dilation of the pupil, blurred vision, problems clearly focusing an object, speech disorders, dizziness, convulsions, stupor, loss of consciousness, coma, yawning, abnormally slow or rapid breathing which could lead to temporarily stopping breathing, failure of the heart to contract effectively (called cardiac arrest).

If you have any further questions on the use of this medicine, ask your dentist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

While you are in your dentist’s office, your dentist will carefully follow the effects of X / Y.

Inform your dentist, doctor or pharmacist immediately if you experience one of the following serious side effects:
- swollen face, tongue or pharynx, difficulty to swallow, hives or difficulties to breath (angioedema)
- rash, itching, swelling of the throat and difficulty breathing: this might be symptoms of an allergic (hypersensitivity) reaction.
- a combination of drooping of the eyelid and constriction of the pupil (Horner's syndrome)

These side effects happen rarely (may affect up to 1 in 1,000 people).
Other side effects not listed above may also occur in some patients.

Common side effects: may affect up to 1 in 10 people:
- inflammation of the gums
- neuropathic pain – pain due to nerve damage
- numbness or reduced sense of touch in and around the mouth
- metallic taste, taste disturbance or loss of taste function
- increased, unpleasant or abnormal sense of touch
- increased sensitivity to heat
- headache
- abnormal rapid heartbeat
- abnormal slow heartbeat
- low blood pressure
- swelling of tongue, lips and gums

Uncommon side effects: may affect up to 1 in 100 people:
- burning sensation
- high blood pressure
- inflammation of the tongue and mouth
- nausea, vomiting, diarrhea
- rash, itching
- pain in the neck or at the site of the injection

Rare side effects: may affect up to 1 in 1,000 people:
- nervousness, anxiety
- facial nerve disorder (facial palsy)
- somnolence
- involuntary eye movement
- double vision, temporary blindness
- drooping of the eyelid, and constriction of the pupil (Horner’s syndrome)
- recession displacement of the eyeball into the orbit (*Enophthalmos)*
- ringing of the ears, over-sensitivity of hearing
- palpitations
- hot flush
- wheezing (bronchospasm), asthma
- difficulty breathing
- exfoliation and ulceration of the gums
- exfoliation of the injection site
- hives (urticarial)
- muscle twitch, involuntary muscle contraction
- fatigue, weakness
- chills

Very rare side effects: may affect up to 1 in 10,000 people:
- persistent loss of sensitivity, extended numbness and loss of taste

Not known: frequency cannot be estimated from the available data
- extremely good mood (euphoria)
- heartbeat coordination problems (conduction disorders, atrioventricular block)
- increased amount of blood in a part of the body leading to congestion of blood vessels
- widening or narrowing of blood vessels
- hoarseness
- difficulty in swallowing
- swelling of cheeks and local swelling
- Burning mouth syndrome
- redness of the skin (erythema)
- abnormally increased sweating,
- worsening of the neuromuscular symptoms in Kearns-Sayre syndrome
- feeling hot or feeling cold
- lock-jaw

Reporting of side effects
If you get any side effects, talk to your dentist, doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of these medicines.

5. How to store X / Y

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store below 25°C.
Do not freeze.
Keep the cartridges in the tightly closed outer carton in order to protect from light.

Do not use this medicine if you notice that the solution is cloudy or discoloured.

The cartridges are intended for single use. Use immediately after the opening of the cartridge. Unused solution must be discarded.

Do not throw away any medicines via wastewater or household waste. Your dentist knows how to throw away medicines no longer used. These measures will help protect the environment.

6. Contents of the pack and other information

What X / Y contains
- The active substances are articaine hydrochloride and adrenaline tartrate.
  - Each cartridge of 1.7-ml of solution for injection of X contains 68 mg of articaine hydrochloride and 8.5 micrograms of adrenaline (as adrenaline tartrate).
  - 1 ml of X contains 40 mg of articaine hydrochloride and 5 micrograms of adrenaline (as adrenaline tartrate).

  - Each cartridge of 1.7-ml of solution for injection of Y contains 68 mg of articaine hydrochloride and 17 micrograms of adrenaline (as adrenaline tartrate).

- 1 ml of Y contains 40 mg of articaine hydrochloride and 10 micrograms of adrenaline (as adrenaline tartrate).

- The other ingredients are sodium chloride, disodium edetate, sodium metabisulfite (E223), sodium hydroxide and water for injections.

What X / Y look like and contents of the pack
X / Y is a clear and colourless solution.
It is packed in single use glass cartridges sealed at the base by a mobile rubber plunger and at the top by a rubber seal kept in place by an aluminium cap.

Box containing glass cartridges 50 x 1.7 ml.
Box containing glass cartridges, self-aspirating 50 x 1.7 ml.
Pack of 4 boxes containing glass cartridges 50 x 1.7 ml.
Pack of 8 boxes containing glass cartridges 50 x 1.7 ml.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

These medicinal products are authorised in the Member States of the EEA under the following names:

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

<[See Annex I - To be completed nationally]>

This leaflet was last revised in {month YYYY}.

<[To be completed nationally]>

Other sources of information

<Detailed information on this medicine is available on the website of {name of MS Agency (link)}>

The following information is intended for healthcare professionals only:

Posology

For all populations, the lowest dose leading to effective anaesthesia should be used. The necessary dosage must be determined on an individual basis.

For a routine procedure, the normal dose for adult patients is of 1 cartridge, but the contents of less of a cartridge may be sufficient for effective anaesthesia. At the discretion of the dentist, more cartridges may be required for more extensive procedures without exceeding the maximum recommended dose.

For most routine dental procedures, it is preferable to use {(Invented) name and associated names (see Annex I)} 40 mg/ml + 5 micrograms/ml.
For more complex procedures, such as requiring pronounced hemostasis, it is preferable to use {(Invented) name and associated names (see Annex I)} 40 mg/ml + 10 micrograms/ml.

Concomitant use of sedatives to reduce patient anxiety:
The maximum safe dose of local anaesthetic may be reduced in sedated patients due to an additive effect on central nervous system depression.

Adults and adolescents (12 to 18 years of age)
In adults and adolescents, the maximum articaine dose is 7 mg/kg with an absolute maximum articaine dose of 500 mg. The maximum articaine dose of 500 mg corresponds to a healthy adult of more than 70 kg body weight.

Children (4 to 11 years of age)
The safety of {(Invented) name and associated names (see Annex I)} in children aged 4 years and below has not been established. No data are available.
The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation.The average effective dose is 2 mg/kg and 4 mg/kg for simple and complex procedures, respectively. The lowest dose providing effective dental anaesthesia should be used. In children aged 4 years (or from 20 kg (44 lbs) of body weight) and above, the maximum dose of articaine is 7 mg/kg only with an absolute maximum dose of 385 mg articaine for a healthy child of 55 kg body weight.

Special populations

Elderly and Patients with renal disorders:
Due to the lack of clinical data, particular precaution should be used in order to administer the lowest dose leading to effective anaesthesia in elderly patients and in patients with renal disorders.
Elevated product plasma levels may occur in these patients in particular after repeated use. In case of required reinjection, patient should be strictly monitored, to identity any sign of relative overdose.

Patients with hepatic impairment
Particular precaution should be used in order to administer the lowest dose leading to efficient anaesthesia in patients with hepatic impairment, in particular after repeated use, although 90% of articaine is first inactivated by unspecific plasma esterases in the tissue and blood.

Patients with plasma cholinesterase deficiency
Elevated product plasma levels may occur in patients with cholinesterase deficiency or under acetylcholinesterase inhibitors treatment since the product is inactivated at 90% by plasmatic esterases. Therefore, the lowest dose leading to effective anaesthesia should be used.

Method of Administration

Infiltration and perineural use in oral cavity.

Local anaesthetics should be injected with caution when there is inflammation and/or infection at the site of the injection. The rate of injection should be very slow (1 ml/min).

Precautions to be taken before handling or administering the medicinal product

This medicinal product should only be used by or under the supervision of physicians or dentists sufficiently trained and familiar with diagnosis and treatment of systemic toxicity. The availability of appropriate resuscitation equipment and medication should be ensured before induction of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies. The patient's state of consciousness should be monitored after each local anaesthetic injection.

When using {(Invented) name and associated names (see Annex I)} for infiltration or regional block anaesthesia, injection should always be made slowly and with prior aspiration.

Special warnings

Adrenaline impairs the flow of blood in the gums, potentially causing local tissue necrosis.
Very rare cases of prolonged or irreversible nerve injury and gustatory loss have been reported after mandibular block analgesia.

Precautions for use

Risk associated with accidental intravascular injection:
Accidental intravascular injection may cause sudden high levels of adrenaline and articaine in the systemic circulation. This may be associated with severe adverse reactions, such as convulsions, followed by central nervous and cardiorespiratory depression and coma, progressing to respiratory and circulatory arrest.
Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the local anaesthetic medicinal product is injected. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Risk associated with intraneural injection:
Accidental intraneural injection may lead the drug to move in retrograde manner along the nerve.
In order to avoid intraneural injection and to prevent nerve injuries in connection with nerve blockades, the needle should always be slightly withdrawn if electric shock sensation is felt by the patient during injection or if the injection is particularly painful. If needle nerve injuries occur, the neurotoxic effect could be aggravated by articaine potential chemical neurotoxicity and the presence of adrenaline as it may impair the perineural blood supply and prevent articaine local wash-out.

Treatment of overdose

The availability of resuscitation equipment and medication should be ensured before administration of regional anaesthesia with local anaesthetics to enable prompt treatment of any respiratory and cardiovascular emergencies.
The seriousness of overdose symptoms should have physicians/dentists to implement protocols that foresee the necessity of timely securing the airway and providing assisted ventilation.
The patient's state of consciousness should be monitored after each local anaesthetic injection.
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately. Change patient position to supine position if necessary.

CNS symptoms (convulsions, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.
Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis may prevent cardiac arrest.
If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and/or inotropic agents should be considered. Children should be given doses commensurate with age and weight.
In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation should be performed.

Special precautions for disposal and other handling

This medicine should not be used if the solution is cloudy or discoloured.
To avoid risk of infection (e.g. hepatitis transmission), syringe and needles used to draw up the solution must always be fresh and sterile.
The cartridges are intended for single use. If only a portion of a cartridge is used, the remainder must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.