

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Espestesin Forte 40 mg/ml + 10 microgram/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

	1 ml solution for injection contains	1 cartridge with 1.7 ml solution for injection contains
Articaine hydrochloride	40 mg	68 mg
Epinephrine (adrenaline) (as hydrochloride)	10 micrograms	17 micrograms
Excipient with known effect		
Sodium sulfite (E 221)	0.6 mg	1.02 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Clear colourless solution with a pH value of 3.6 to 4.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local and loco-regional anaesthesia in dental procedures.

Espestesin Forte is indicated in adults, adolescents and children above 4 years of age (or from 20 kg 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 Espestesin.

For more complex procedures, such as requiring pronounced hemostasis, it is preferable to use Espestesin Forte.

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 for Espestesin Forte:

Patient body weight (kg)	Maximum dose of articaine hydrochloride (mg)	Dose of epinephrine (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 Espestesin Forte 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 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 for Espestesin Forte:

Patient body weight (kg)	Maximum dose of articaine hydrochloride (mg)	Dose of epinephrine (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 identify 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 Espestesin Forte 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 epinephrine 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 epinephrine. (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 anaesthesia 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

Espestesin Forte 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:

Espestesin Forte 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 identify any sign of relative overdose (see section 4.9).

Therefore, the lowest dose leading to effective anaesthesia should be used.

The use of Espestesin over Espestesin Forte 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/epinephrine 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 epinephrine.
- 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 epinephrine.
- Patients with susceptibility of acute angle-closure glaucoma: This medicinal product should be used cautiously due to the presence of epinephrine.

The lowest dose leading to effective anaesthesia should be used.

This medicinal product must be used safely and effectively under appropriate conditions:

Epinephrine 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 sulfite (E 221), that may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge, that is to say 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 epinephrine 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 epinephrine 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 epinephrine

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 epinephrine 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, linezolid):

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 epinephrine 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 epinephrine effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with articaine 40 mg/ml + epinephrine 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 epinephrine 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. Epinephrine 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, epinephrine can reduce uterine perfusion.

During pregnancy, Espestesin Forte should only be used after a careful analysis of the benefit-to-risk ratio has been made.

On account of its lower epinephrine content, the use of Espestesin over Espestesin Forte should be preferred.

Breast-feeding

As a result of the rapid drop in serum levels and rapid elimination, clinically relevant quantities of articaine are not found in breast milk. Epinephrine 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 + epinephrine 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 epinephrine hydrochloride 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 Espestesin Forte (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 / epinephrine 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 summary of adverse reactions:

The reported adverse reactions come from spontaneous reporting, clinical studies and literature.

The frequencies classification follows the convention:

Very common ($\geq 1/10$)
Common ($\geq 1/100$ to $< 1/10$)
Uncommon ($\geq 1/1,000$ to $< 1/100$)
Rare ($\geq 1/10,000$ to $< 1/1,000$)
Very rare ($< 1/10,000$)
Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Common	Gingivitis
Immune system disorders	Rare	Allergic ¹ , anaphylactic/anaphylactoid reactions ⁵
Psychiatric disorders	Rare	Nervousness (restlessness)/anxiety ⁴
	Not known	Euphoric mood
Nervous system disorders	Common	Neuropathy: Neuralgia (neuropathic pain) Hypoesthesia / numbness (oral and perioral, facial) ³ Hyperesthesia Dysesthesia (oral and perioral), <i>including</i> 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, transient paresthesia) after mandibular or inferior

		alveolar nerve blocks
	Not known	Presyncope/syncope (depressed level or loss of consciousness, dizziness) Convulsion/grand mal convulsion
Eye disorders	Rare	Diplopia (paralysis of oculomotor muscles) Visual impairment (temporary blindness, visual acuity reduced) Ptosis Miosis Enophthalmos Mydriasis Eye pain
Ear and labyrinth disorders	Rare	Hyperacusis Tinnitus
Cardiac disorders	Common	Bradycardia Tachycardia
	Rare	Palpitations
	Not known	Conduction disorders (atrioventricular block, cardiac arrest)
Vascular disorders	Common	Hypotension (with possible circulatory collapse)
	Uncommon	Hypertension
	Rare	Hot flush, Pallor
	Not known	Local / Regional hyperaemia Vasodilatation Vasoconstriction
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm / asthma Dyspnoea
	Not known	Dysphonia (Hoarseness)
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 reaction
	Rare	Injection site exfoliation/necrosis Fatigue, asthenia (weakness)/ Chills
	Not known	Local swelling Feeling hot, Feeling cold

c) Description of selected adverse events:

¹ Allergic reactions should not be mistaken with syncopal episodes (cardiac palpitations due to epinephrine). The term allergic reactions also cover the following preferred terms: hypersensitivity, including Type IV hypersensitivity reaction, and allergy test positive.

² A 2 week delay in the onset of facial paralysis has been described following administration of articaine combined with epinephrine, 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).

⁵ The term "anaphylactic reaction" covers the following preferred terms: anaphylactic shock and Type I hypersensitivity.

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 years old children, due to the prolonged soft tissue anaesthesia.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

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 epinephrine:

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.

Epinephrine, as vasoconstrictor, acts directly on both α - and β -adrenergic receptors; β -adrenergic effects predominate.

Epinephrine prolongs the effect duration of the articaine, and reduces the risk of excessive uptake of articaine into the systemic circulation.

Clinical efficacy and safety:

Espestesin Forte has an onset of 1.5- 1.8 min for infiltration and 1.4-3.6 min for nerve block.

The anaesthetic duration of Espestesin Forte 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 epinephrine 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 α/β -globulins (62.5-73.4%). Binding to γ -globulin (8.6-23.7%) was much lower. Epinephrine 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. Epinephrine exhibits sympathomimetic effects.

Subcutaneous injections of articaine combined with epinephrine 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.

Teratogenicity was observed in animals treated with epinephrine 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 + epinephrine 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 epinephrine.

Contradictory findings were raised from in-vitro and in-vivo genotoxicity studies with epinephrine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium sulfite (E221)

Sodium chloride

Hydrochloric acid 14% (for pH adjustment)

Sodium hydroxide solution 9% (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

Use immediately after the opening of the cartridge.

6.4 Special precautions for storage

Store below 25°C. Keep the cartridges in the original package in order to protect from light.

6.5 Nature and contents of container

Cartridge made of colourless neutral glass I.

Stopper and rubber disc are made of butyl rubber.

Gold coloured aluminium cap made of aluminium-iron-silicon-alloy.

Tin with 50 cartridges of each containing 1.7 ml.

6.6 Special precautions for disposal and other handling

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.

Cartridges should be carefully taken out of the tin in order to avoid cutting injuries

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.

7 MARKETING AUTHORISATION HOLDER

Pierrel S.p.A.

Strada Statale Appia 7 Bis 46/48

Capua

CE

81043

Italy

8 MARKETING AUTHORISATION NUMBER

PA25244/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2003

Date of last renewal: 16 January 2011

10 DATE OF REVISION OF THE TEXT

November 2023