SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Orabloc
40 mg/ml + 0,01 mg/ml solution for injection
Articaine hydrochloride and adrenaline (epinephrine) 1:100 000

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONTIVNI I KVANTITATIVNI SASTAV

1 ml solution for injection contains 40 mg articaine hydrochloride and 0.01 mg adrenaline (epinephrine) as adrenaline tartrate.

One cartridge of 1.8 ml of solution for injection contains 72 mg articaine hydrochloride and 0.018 mg adrenaline (epinephrine) as adrenaline tartrate

Excipients with known effect:
Contains sodium metabisulphite (E223) 0.5 mg/ml and sodium 4.5 mg/ml..

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution for injection.
The pH of the solution ranges from 3.0 to 4.5.
Osmolarity: 270 mOsm/KG

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orabloc is indicated in adults, adolescents and children of 4 years and older for local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry:

- mucosal and bone surgery requiring stronger ischaemia,
- dental pulp surgery (amputation and extirpation),
- extraction of fractured teeth (osteotomy),
- protracted surgical interventions,
- percutaneous osteosynthesis,
- cystectomy,
- mucogingival interventions (gingiva),
- apicoectomy.

4.2 Posology and method of administration

Posology

For uncomplicated forceps extraction of the upper teeth where no inflammation is present, a vestibular injection of 1.8 ml per tooth is usually sufficient. In isolated cases, an additional vestibular injection of 1-1.8 ml may be necessary to achieve complete anaesthesia. Injection via the painful palatine route is normally not necessary.

Where the palate requires incision or suture, a palatine depot of about 0.1 ml per puncture is sufficient. Where multiple extractions of adjacent teeth are necessary, it is possible in most cases to reduce the number of vestibular injections required.

In uncomplicated forceps extraction of lower premolars where no inflammation is present, injection of 1.8 ml per tooth is usually sufficient. However, if the anaesthesia is incomplete, an additional vestibular injection of 1-1.8 ml is recommended. Conventional mandibular anaesthesia is indicated

only where the above mentioned procedure does not result in a complete anaesthesia..

For surgical operations, it is recommended that the dose of Orabloc be adjuste individually based on the operation's severity and duration.

Over the course of treatment, adults may be given up to 7 mg articaine per kg body weight. Using the aspiration technique, doses of up to 500 mg (equivalent to 12.5 ml of solution for injection) were well tolerated.

Elderly patients and patients with severe hepatic and renal dysfunction
Increased plasma articaine levels may occur in elderly patients and in patients with severe hepatic and renal dysfunction. In such patients, particular care should be taken to use the minimum dose needed to achieve required anaesthesia.

Paediatric population
When using Orabloc in children and adolescents, the minimum volume necessary to achieve adequate anaesthesia should be used; the injection amount should be individually tailored to the age and weight of the child and adolescent.

A maximum dose of 5 mg articaine per kg of body weight should not be exceeded.

This product has not been studied in children less than 1 year old.

Način primjene
Orabloc is intended for use in the oral cavity (dental use).

Before injection, aspiration is always recommended to avoid intravascular injection. Aspiration should be performed in two stages, i.e. needle rotation by 90° or even better by 180°.

Major systemic reactions as a result of accidental intravascular injection can be avoided in most cases by an injection technique – after aspiration, slow injection of 0.1–0.2 ml and slow application of the rest – not earlier than 20–30 seconds later.

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

For single use. Any unused solution should be discarded.
This medicinal product should not be used if cloudy or discoloured.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

On account of the effect of the articaine content, Orabloc must not be used in:
- hypersensitivity to other local anaesthetics of the amide type,
- severe cardiac impulse formation and conduction disturbances (e.g. 2nd or 3rd degree AV block, marked bradycardia),
- acute decompensated heart failure (acute congestive heart failure),
- severe hypotension,
- children under 4 years of age..

On account of the effect of the adrenaline (epinephrine) content, Orabloc must not be used in:
- anaesthesia of the terminal nerve branches,
- patients with narrow-angle glaucoma,
- patients with hyperthyroidism,
- patients with paroxysmal tachycardia or absolute arrhythmias with rapid heart rate,
- patients with recent (3 to 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),
- patients with phaeochromocytoma,
- patients with severe hypertension,
- concomitant treatment with tricyclic antidepressants or MAO inhibitors, as these active substances can intensify the cardiovascular effects of adrenaline (epinephrine). This can occur up to 14 days after MAO inhibitor treatment has ended.

Intravenous use is contraindicated.

Orabloc must not be used in persons with bronchial asthma with hypersensitivity to sulphites. In such individuals, Orabloc may precipitate acute allergic reactions with anaphylactic symptoms, such as bronchospasm.

4.4 Special warnings and precautions for use

In patients with cholinesterase deficiency, Orabloc must only be given in the presence of compelling indications, since its action is likely to be prolonged and may sometimes be too strong

Orabloc must be used with particular caution in cases of:
- blood coagulation disturbances,
- severe renal or hepatic dysfunction,
- concomitant treatment with halogenated inhalation anaesthetics (see section 4.5),
- history of epilepsy (see section 4.8).

and use of Orabloc 1:200,000 solution for injection
over Orabloc 1:100,000 solution for injection should be considered on account of its lower adrenaline (epinephrine) content of 0.005 mg/ml in patients with:
- cardiovascular diseases (e.g. heart failure, coronary heart disease, angina pectoris, history of myocardial infarction, cardiac arrhythmia, hypertension),
- arteriosclerosis,
- cerebral circulation disturbances, history of strokes,
- chronic bronchitis, pulmonary emphysema,
- diabetes mellitus,
- severe anxiety

Injection into an inflamed (infected) area is discouraged (increased uptake of Orabloc with reduced efficacy).

Before using this product it is necessary to ask the patient questions on medical history, concomitant treatment and to keep verbal contact with patient, and to practice an injection test with 5 or 10% of the dose in case of risk of allergy.

To avoid occurrence of adverse effects the following must be taken into account:
- choose the lowest possible dose,
- before injection, aspiration in two stages (to avoid inadvertent intravascular injection).

Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available (Oxygen, anticonvulsive drugs as benzodiazepines or barbiturates, muscle relaxants, atropin and vasopressin or epinephrine (adrenalin) in case of severe allergic or anaphylactic reactions).

It is recommended that the patient refrain from eating until the anaesthesia has worn off.

Paediatric population
Carers of young children should be warned of the risk of accidental soft tissue injury due to self-biting, due to prolonged soft tissue numbness.

This medicinal product contains metabisulphite (E223) which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-

free'.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations of different anaesthetics cause additive effects on cardiovascular system and CNS.

The blood-pressure-increasing effects of sympathomimetic-type vasoconstrictors (such as adrenaline) may be intensified by tricyclic antidepressants or MAO inhibitors and these are therefore contraindicated (see section 4.3).

For concomitant use of non cardioselective beta-blockers, see section 4.3.

Adrenaline (epinephrine) may inhibit the release of insulin in the pancreas, thereby attenuating the effect of oral antidiabetics.

Certain inhalation anaesthetics, such as halothane, may increase myocardial sensitivity to catecholamines, and may therefore precipitate arrhythmias following administration of Orabloc.

Phenothiazines can influence the blood-pressure-increasing effects of epinephrine. Therefore concomitant treatment should be avoided. If concomitant treatment is necessary patients should be monitored carefully.

It should be remembered that, in patients receiving anticoagulation treatment (e.g. heparin or acetylsalicylic acid), inadvertent vascular puncture during local anaesthesia may lead to serious bleeding, and that the tendency to bleed is generally increased in such patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of the use of articaine in pregnant women, except during childbirth. Animal studies do not indicate that articaine has direct or indirect harmful effects on pregnancy, embryonal/foetal development, birth or postnatal development. Animal studies have shown that adrenaline (epinephrine) is toxic to reproduction at doses higher than maximal recommended dose (see section 5.3).

Adrenaline (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, adrenaline (epinephrine) can reduce uterine perfusion. During pregnancy, Orabloc should only be used after a careful analysis of the benefit-to-risk ratio has been made.

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 (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.

Fertility

Animal studies with articaine 40 mg/ml + adrenaline (epinephrine) 0.01 mg/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

After application of Orabloc the dentist must decide when a patient is capable again of operating a vehicle or machinery..

Apprehension and operation related stress may affect performance capabilities; although, in relevant tests, local anaesthesia with articaine caused no discernible impairment in normal driving ability.

4.8 Undesirable effects

The following categories are used for classifying the frequency of undesirable effects:

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)
Very rare (<1/10.000)
Not known (cannot be estimated from the available data)

Immune system disorders
Not known: Allergic or allergy-like hypersensitivity type reactions. These may manifest themselves as oedematous swelling and/or inflammation at the injection site or manifestations appearing independently of the site may include skin reddening, itching, conjunctivitis, rhinitis, facial swelling (angioedema) with swelling of the upper and/or lower lip and/or cheeks, glottal oedema with globus pharyngis and difficulty in swallowing, urticaria and difficulty in breathing which may progress to anaphylactic shock.

Nervous system disorders
Common: paresthesia, hypoesthesia; headaches, due presumably to the adrenaline component.
Uncommon: dizziness
Učestalost nije poznata:

- Dose-related (particularly at excessively high dosages or after inadvertent intravascular injection), central nervous system reactions may occur: agitation, nervousness, stupor sometimes progressing to loss of consciousness, coma, respiratory disorders sometimes progressing to respiratory arrest, muscular tremor and muscular twitching sometimes progressing to generalised convulsions.
- Nerve lesions (e.g. facial nerve paresis) and reduced gustatory sensitivity in the orofacial regionare not side effects specific to articaine. However, such reactions are theoretically possible with any dental intervention, due to anatomical conditions in the injection area or incorrect injection techniques.

Eye disorders
Not known: Temporary visual disturbances (blurred vision, blindness, double vision) occurring during or shortly after injection of local anaesthetics in the area of the head.

Cardiac disorders
Uncommon: tachycardia
Not known: cardiac arrhythmias, rise in blood pressure, hypotension, bradycardia, cardiac failure and shock (possibly life-threatening).

Respiratory, thoracic and mediastinal disorders
Not know: respiratory dysfunction (tachypnea, bradypnea) that may lead to apnea.

Gastrointestinal disorders
Common: Nausea, vomiting..

General disorders and administration site conditions:
Not known: inadvertent intravascular injection may lead to the development of ischaemic zones in the injection site, sometimes progressing to tissue necrosis (see also section 4.2).

Special notes
On account of its sodium metabisulphite content, the product can precipitate hypersensitivity reactions, particularly in patients with bronchial asthma. Such reactions may manifest in vomiting, diarrhoea, wheezing, acute asthma attacks, impaired consciousness or shock..

Paediatric population
In published studies, the safety profile was similar in children and adolescents from 4 to 18 year old

compared to adults. However, accidental soft tissue injury was observed more frequently (in up to 16% of children), especially in 3 to 7 year old children, due to the prolonged soft tissue anaesthesia. In a retrospective study of 211 children aged 1 to 4 years of age, dental treatment was carried out using up to 4.2 ml of 4% articaine + 0.005 mg/ml or 0.01 mg/ml adrenaline (epinephrine), with no reported side effects.

Reporting of suspected adverse reactions

Reporting suspected adverse drug reaction, after placing the drug on the market, is of great importance for the formation of a more complete picture of the safety profile of the drug, i.e. to form a better relation assessment of benefit/risk in the therapeutic use of the drug.

The process of reporting suspected adverse drug reaction contributes to the continuous monitoring of the benefit/risk relation assessment and adequate safety profile of the drug. Health professionals are asked to report any suspected adverse drug reaction directly to The Agency for Medicinal Products and Medical Devices Bosnia and Herzegovina. Application can be sent:

- Through a software application for reporting adverse drug reaction for human use (IS Pharmacovigilance) with more information available in our Main Office for Pharmacovigilance, or
- Through the appropriate application form for reporting suspected adverse drug reaction, which can be found on the website of the Agency for Medicinal Products: www.almbih.gov.ba. Complete application form can be posted to the address The Agency for Medicinal Products and Medical Devices Bosnia and Herzegovina (ALMBIH), Veljka Mlađenovića bb, Banja Luka, or mailed (e-mail address: ndl@almbih.gov.ba)"

4.9 Overdose

a) Symptoms of over dosage

CNS stimulation: restlessness, anxiety, confusion, hyperpnoea, tachycardia, rise in blood pressure with facial reddening, nausea, vomiting, tremor, twitching, tonicclonic seizures.

CNS depression: dizziness, impairment of hearing, loss of ability to speak, loss of consciousness, muscle atony, vasomotor paralysis (weakness, pallor), dyspnoea, death due to respiratory paralysis.

Cardiovascular depression: bradycardia, arrhythmia, ventricular fibrillation, fall in blood pressure, cyanosis, cardiac arrest.

b) Emergency measures and antidotes

At the first signs of side effects or intoxication, e.g. dizziness, motor restlessness, or stupor, the injection should be stopped and the patient placed in a horizontal position. The patient's airway should be kept clear and pulse and blood pressure monitored.

It is recommended, including when the symptoms of intoxication seem not to be severe, to insert an I.V. catheter, for immediate intravenous injections when necessary.

In respiratory disorders, depending on their severity, the administration of oxygen, as well as – where necessary – that of artificial respiration are recommended, as is where necessary, the performance of endotracheal intubation and controlled ventilation.

Muscular twitching or generalised convulsions may be removed by intravenous injection of a short acting antispasmodic (e.g. suxamethonium chloride, diazepam).
Artificial respiration (oxygen) is also recommended

A fall in blood pressure, tachycardia, or bradycardia may be corrected simply by placing the patient in a horizontal or slightly 'head-down' position.

In severe circulatory disturbances and shock – regardless of cause – the following emergency measures should be immediately implemented after stopping the injection:

- place the patient in a horizontal or 'head-down' position and keep the patient's airways clear (oxygen insufflation),
- set up an intravenous infusion (balanced electrolyte solution),

- intravenous administration of a glucocorticoid (e.g. 250-1000 mg prednisolone or the equivalent amount of a derivative, e.g. methylprednisolone),
- volume substitution (additionally, if necessary, plasma expander, human albumin).

If circulatory collapse appears imminent and bradycardia worsens, intravenous adrenaline (epinephrine) should be given immediately.
After diluting 1 ml of a
commercial 1:1,000 adrenaline (epinephrine) solution to 10 ml (a 1:10,000 adrenaline (epinephrine) solution can be used instead), 0.25 - 1 ml of the solution (= 0.025 - 0.1 mg adrenaline (epinephrine)) is injected slowly with monitoring of pulse and blood pressure (caution: cardiac arrhythmias). Do not exceed 1 ml (0.1 mg adrenaline (epinephrine)) per single intravenous injection. Where additional amounts of adrenaline are required, recommendation is given to administering these together with the infusion solution (adjust drip rate according to pulse rate and blood pressure).

Severe tachycardia and tachyarrhythmias may be treated with anti-arrhythmic drugs, but not with noncardioselective beta-blockers, e.g. propranolol (see section 4.3). In such cases, oxygen must be given and circulation monitored.

Increase of blood pressure in hypertensive patients must be treated with peripheral vasodilators, if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local;
Amides.
ATC code: N01BB58.

Orabloc is an acid amide-type local anaesthetic used for terminal and nerve-block anaesthesia in dentistry. It is fast-acting (latency time 1-3 min) with a potent analgesic effect and good tissue tolerability.

The duration of effective anaesthesia is about 75 min for Orabloc 1:100 000.

The mechanism of action of articaine is assumed to be based on inhibition of conduction in nerve fibres, due to blockade of voltage-dependent Na+ channels in the cell membrane..

Its extremely low adrenaline (epinephrine) concentration and high intensity of action make Orabloc 0.005 mg/ml suitable for use in patients with cardiovascular diseases.

Paediatric population
In children 3.5 to 16 years old, clinical studies including up to 210 patients, have shown that 4% articaine + 0.005 mg/ml adrenaline (epinephrine) at doses up to 5 mg/kg and 4% articaine + 0.010 mg/ml adrenaline (epinephrine) at doses up to 7 mg/kg provided successful local anaesthesia , if given by (mandibular) infiltration or (maxillary) nerve block. The anaesthesia duration was similar for all age groups and depended on the volume administered.

5.2 Pharmacokinetic properties

In serum, articaine is bound to plasma-proteins at 95%. The elimination half-life after intraoral submucosal injection is 25.3 ± 3.3 min. 10% of articaine is metabolised in the liver, mainly by plasma and tissue esterases. Articaine is subsequently excreted via the renal route, mainly as articainic acid.

In children, overall exposure after vestibular infiltration is similar to those in adults, but maximum serum concentration is reached faster..

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 (epinephrine) exhibits sympathomimetic effects.

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 (rat) and 12.5 mg/kg (rabbit). Adrenaline (epinephrine) showed reproductive toxicity in animals at doses ranging from 0.1 to 5 mg/kg (several folds the maximal dose of adrenaline (epinephrine) when using Orabloc) with evidence of congenital malformations and impaired uteroplacental perfusion.

In embryofoetotoxicity studies with articaine and adrenaline (epinephrine), no increase in malformations were observed at daily s.c. doses of articaine up to 80 mg/kg (rat) and 40 mg/kg (rabbit).
In a fertility and early embryonic development study in rats no adverse effects on male or female fertility were noted at doses causing parental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium metabisulfite (E223)
Hydrochloric acid 2% (for pH adjustment)
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of unopened product: 2 years
Shelf life after first opening: Use immediately.

The solution must be clear and colorless. The product should not be used if it has color impurities or is cloudy.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Clear glass cartridges (Type I) closed at one end with a bromobutylic rubber plunger
and at the other with an aluminium cap and rubber seal.
The cartridges are packaged in PVC blisters (10 cartridges/blister); the blisters are packaged in a cardboard box (5 blisters with 10 cartridges).

6.6 Special precautions for disposal

As for any cartridge, the rubber seal (diaphragm) will be disinfected just before use with either pharmaceutical grade ethyl alcohol (70%) or pharmaceutical grade Isopropyl alcohol (90%). Patrone se ne moraju uranjati u navedene rastvore. The cartridges must not be immersed in the above solutions.
Do not mix the injectable solution with other products in the same syringe.

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

6.7 Regime

Medicinal product used in the secondary or tertiary health institution.

7 NAME AND ADDRESS OF THE MANUFACTURER (administrative headquarter), MANUFACTURER OF THE FINISHED PRODUCT (batch release site) I MARKETING AUTHORIZATION HOLDER

Manufacturer (administrative headquarter and batch release site)
Pierrel S.p.A.
Strada Statale Appia, 7 BIS 46/48 – 81043 Capua (CE)
Italy

Marketing authorization holder
PTD "MGM FARM, d.o.o. Kakanj
311. Lahke brigade broj 97, Kakanj

8 Number and date of the approval

04-07.3-1-1062/20 from 09.11.2021