

# Xylonor Epinephrine



**1) Name of the medicinal product:** XYLONOR EPINEPHRINE

**2) Qualitative and quantitative composition:**

1 ml of solution for injection contains 20 mg of Lidocaine Hydrochloride (as Monohydrate) and 12.5 micrograms (1:80,000) of Epinephrine (as Bitartrate).

Epinephrine Bitartrate and also called Adrenaline Tartrate. Both names are synonyms.

One cartridge of 1.7 ml of solution for injection contains 34 mg of Lidocaine Hydrochloride (as Monohydrate) and 21.25 micrograms of Epinephrine (as Bitartrate).

**Excipient(s) with known effect:** This medicinal product contains 1.20 mg/ml Potassium Metabisulfite (E224) [equivalent to 0.422 mg/ml Potassium (0.0108 mmol/ml)], and 2.602 mg/ml Sodium [0.11 mmol/ml].

For the full list of excipients, see section 6.1.

**3) Pharmaceutical Form:** Solution for injection.

**4) CLINICAL PARTICULARS:**

**4.1) Therapeutic indications:**

For the production of local anaesthesia for dental procedures by infiltration or nerve block injections.

**4.2) Posology and method of administration:**

- **Adults:** A single cartridge is generally sufficient. Two are used in case of large interventions. However, three may be used if deemed necessary for prolonged procedures.
- **Adolescents between 14 and 17, and the elderly:** Usual dose 1.7 ml (1 cartridge). Do not exceed 3.4 ml (2 cartridges) in usual cases.
- **Children between 6 and 14:** Usual dose 1.35 ml (4/5 of a cartridge). Do not exceed 2.7 ml (1½ cartridge) in usual cases.
- **Children between 3 and 6:** 0.9 to 1.7 ml (½ to 1 cartridge).

**Do not use under 3 years of age.**

**Method of administration:** Infiltration or nerve block injection.

Before injection, aspiration should always be performed to avoid intravascular injection and if required, the needle repositioned until no return of blood can be elicited by aspiration. The absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Major systemic reactions as a result of accidental intravascular injection can be avoided in most cases by an injection technique after aspiration with a slow injection.

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.

The medicinal product should not be used if cloudy or discoloured.

For information relevant to the handling of the product, see section 6.6.

**4.3) Contraindications**

- Hypersensitivity to lidocaine (or to any local anaesthetic agent of the amide type) or to adrenaline or to any of the excipients listed in section 6.1.

**Due to lidocaine:**

- Severe conduction disturbances (e.g., severe bradycardia, 2nd / 3rd degree AV blocks)
- Acute intermittent porphyria

**Due to epinephrine (adrenaline):**

- Uncontrolled /severe hypertension
- Persistent / refractory tachyarrhythmia
- Pheochromocytoma

**4.4) Special warnings and precautions for use:**

Before using this medicinal product, it is important:

- To make inquiries into the patient's diathesis, current therapies and history;
- To maintain verbal contact with the patient;
- To have resuscitative equipment at hand (see section 4.9).

**Special warnings: This product must be used with caution in:**

**Patients with cardiovascular disorders:**

- Peripheral vascular disease
- Arrhythmias particularly of ventricular origin
- Heart failure
- Hypotension

The product should be administered with caution in patients with impaired cardiac function since they may be less able to compensate changes due to the prolongation of atrio-ventricular conduction.

**Patients with *myasthenia gravis*:** The lowest dose leading to effective anaesthesia should be used as these patients are particularly sensible to the effect of local anaesthetics.

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

**Patients with hepatic disease:** The lowest dose leading to efficient anaesthesia should be used, see section 4.2.

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

**Patients with thyrotoxicosis:** The lowest dose leading to effective anaesthesia should be used.

**Patients with coronary artery disease and valvular cardiac disease:** The lowest dose leading to effective anaesthesia should be used.

**Patients receiving treatment with antiplatelets / anticoagulants:** The increased risk of severe bleeding after accidental vessel puncture and during oro-maxillo-facial surgery should be considered. INR monitoring should be increased in patients under anticoagulants.

**Patients with uncontrolled diabetes:** This product should be used cautiously due to hyperglycemic effect of epinephrine (adrenaline).

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

**Patients under the influence of illicit drug:** The efficacy of this product may be decreased in these patients.

**Elderly patients:** Dosages should be reduced in elderly patients over 70 years old (lack of clinical data).

**The product must be used safely and effectively under appropriate conditions:** Epinephrine (Adrenaline) impairs the flow of blood in the gums, potentially causing local tissue necrosis.

The local anaesthetic effects may be reduced if the product is injected into an inflamed or infected area.

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 sensation is restored.

**Precautions for use:**

**Risk associated with an accidental intravascular injection:** Accidental intravascular injection (e.g.: inadvertent intravenous injection into the systemic circulation, inadvertent intravenous or intra-arterial injection in the head area and neck area) may be associated with severe adverse reactions, e.g., convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest, due to the sudden high level of adrenaline and / or lidocaine in the systemic circulation.

**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 lidocaine's potential chemical neurotoxicity



and the presence of adrenaline as it may impair the perineural blood supply and prevent lidocaine local wash-out.

**Risk of Takotsubo cardiomyopathy or stress-induced cardiomyopathy:** Stress cardiomyopathy induced by injected catecholamines has been reported.

Because of the presence of adrenaline, precautions and monitoring should be enhanced in the following situations: patients stressed prior to dental procedure or conditions of use which may contribute to induce a systemic passage of adrenaline e.g. an administered dose higher than recommended or in case of an accidental intravascular injection. Any previous knowledge of such underlying conditions in patients requiring dental anaesthesia should be minded and a minimal dose of local anaesthetic with vasoconstrictor used.

The medicinal product contains potassium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.

The medicinal product contains potassium, less than 1 mmol (39 mg) for a maximal dose of 16 ml, i.e. essentially 'potassium-free'.

The medicinal product contains 0.1132 mmol/ml (2.602 mg/ml) sodium (main component of cooking/table salt). This is equivalent to approximately 0.665% of the recommended maximum daily dietary intake of sodium for an adult.

The maximum recommended dose of this medicinal product (3 cartridges equivalent to 5.1 ml) contains 0.5773 mmol (13.27 mg) sodium, which is equivalent to 3.39% of the recommended maximum daily intake of sodium for an adult.

Concomitant use of the other medicinal products may require thorough monitoring (See section 4.5).

#### 4.5) Interaction with other medicinal products and other forms of interaction:

##### **Interactions that are not recommended:**

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

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

**Additive interactions with other local anaesthetics:** Toxicity of local anaesthetics is additive.

This point is considered as not relevant with regard to dental anaesthesia doses and blood levels in adults, but it is a concern in children. The total dose of administered lidocaine should not exceed the maximum recommended dose.

**Opioid sedatives (central nervous system depressants):** Reduced doses of this product should be used due to potential additive CNS effects of lidocaine and sedatives.

**Inhibitors of metabolism** (e.g. *cimetidine*): Increased serum levels of amide anaesthetics have been reported after concomitant administration of *cimetidine*.

**Halogenated volatile anaesthetics** (e.g.: halothane): Reduced doses of this product should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia. The patient's hemodynamic status should be closely monitored.

**Non-selective beta-adrenergic blockers** (e.g., propranolol, nadolol): Reduced doses of this product should be used due to possible increase in blood pressure. Close cardiovascular monitoring is recommended.

**(TCAs) Tricyclic antidepressants** (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline): Dose and rate of administration of this product should be reduced due to strengthening of adrenaline activity. Close cardiovascular monitoring is recommended.

**MAO inhibitors** [both *A-selective MAO inhibitors* (e.g., brofaromine, moclobemide, toloxatone) and *non-selective MAO inhibitors* (e.g., phenelzine, tranylcypromine, linezolid)]: Use under strict medical supervision due to possible potentialization of the effects of adrenaline.

**(COMT inhibitors) Catechol-O-methyl transferase inhibitors** (e.g., entacapone, tolcapone): Arrhythmias, increased heart rate and blood pressure variations may occur. Cardiovascular monitoring is recommended.

**Drugs with combination of adrenergic-serotonergic effect** (e.g., venlafaxine, milnacipran, sertraline): Dose and rate of administration of this product should be reduced due to additive or synergistic effects on blood pressure and heart rate. Cardiovascular monitoring (preferably by ECG) is recommended.

**Drugs causing arrhythmias in combination with adrenaline** (e.g., antiarrhythmics like digitalis, quinidine): Dose of administration of this product should be reduced due to additive or synergistic effects on heart rate. Careful aspiration prior to administration and cardiovascular monitoring (ECG) are recommended.

**Ergot-type oxytocic drugs** (e.g., methysergide, ergotamine, ergonovine): Use this 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) **and other sympathomimetics** (e.g., isoproterenol, levothyroxine, methyl dopa, antihistamines (such as chlorpheniramine, diphenhydramine): Risk of adrenergic toxicity. Reduced doses of this product should be used. If cocaine has been used within 24 hours, the planned dental treatment should be postponed.

**Phenothiazines** and other neuroleptics: Use under strict medical supervision and cardiovascular monitoring in case of patients with hypotension due to possible inhibition of adrenaline effect.

#### 4.6) Fertility, pregnancy and lactation:

**Pregnancy:** No effects during pregnancy are anticipated, since systemic exposure to lidocaine and adrenaline is negligible. This product can be used during pregnancy. Refer to section 5.3.

**Breastfeeding:** Lidocaine/metabolites are excreted in human milk, but at therapeutic doses of this product no effects on the breastfed newborns/infants are anticipated.

**Fertility:** No adverse effects on fertility were observed in preclinical studies.

**4.7) Effects on ability to drive and use machines:** Lidocaine in combination with adrenaline solution may have minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of this product (see section 4.8). Patients should not leave the dental office within 30 minutes following the dental procedure.

#### 4.8) Undesirable effects:

**a) Summary of the safety profile:** Adverse reactions following administration of the product are similar to those observed with other amide local anaesthetics combined with vasoconstrictors.

These adverse reactions are, in general, dose-related and may result from high plasma levels caused by overdose, rapid absorption or unintended intravascular injection. They may also result from hypersensitivity, idiosyncrasy, or diminished tolerance by the specific patient. Nervous system disorders, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.

Serious adverse reactions are generally systemic. The presence of epinephrine (adrenaline) increases the product's safety profile due to its sympathomimetic effects.

##### **b) Tabulated list of adverse reactions:**

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

By convention, frequency of initial signs of CNS or CVS toxicity is considered as rare.

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 ( $< 1/10,000$ ) and "Not known (cannot be estimated from the available data)".

| MedDRA system Organ Class                       | Frequency | Adverse Reactions   |
|---|-----------|---|
| Infections and infestations                     | Not known | Gingivitis  |
| Immune system disorders                         | Rare      | Hypersensitivity <sup>1</sup><br>Anaphylactic / anaphylactoid reactions <sup>1</sup>  |
| Psychiatric disorders                           | Rare      | Confusional state   |
|   | Very rare | Euphoric mood<br>Anxiety / Nervousness / Agitation / Restlessness   |
| Nervous system disorders                        | Common    | Neuropathy peripheral <sup>2</sup> :<br>Neuralgia (neuropathic pain)<br>Headache<br>Dizziness (light headedness)<br>Tremor  |
|   | Rare      | Deep CNS depression:<br>Loss of consciousness<br>Convulsion (including tonic clonic seizure)<br>Somnolence  |
| Eye disorders <sup>4</sup>                      | Rare      | Visual impairment<br>Vision blurred<br>Accommodation disorder   |
| Ear and labyrinth disorders                     | Very rare | Tinnitus  |
| Cardiac disorders                               | Common    | Palpitations<br>Tachycardia   |
|   | Very rare | Conduction disorders,<br>atrioventricular block<br>Bradyarrhythmia<br>Cardiac arrest<br>Tachyarrhythmia (including ventricular extrasystoles and ventricular fibrillation) <sup>5</sup> |
| Vascular disorders                              | Common    | Hypotension (with possible circulatory collapse)<br>Hypertension<br>Pallor (local, regional, general)   |
|   | Very rare | Vasodilatation<br>Vasoconstriction<br>Hot flush   |
| Respiratory, thoracic and Mediastinal disorders | Common    | Dyspnoea  |
|   | Rare      | Bronchospasm / asthma   |
|   | Not known | Respiratory depression <sup>3</sup><br>Apnoea (respiratory arrest)  |
| Gastrointestinal disorders                      | Uncommon  | Nausea<br>Vomiting  |
|   | Not known | Gingival / oral mucosal exfoliation (sloughing) / ulceration / necrosis <sup>6</sup><br>Dysphagia <sup>1</sup> , Recurrent aphthous stomatitis,<br>Glossitis <sup>7</sup> , Diarrhoea   |

|  |           |   |
|--|-----------|---|
| Skin and subcutaneous tissue disorders               | Uncommon  | Rash (eruption)<br>Pruritus (itching)   |
|  | Rare      | Angioedema <sup>1</sup> (oedema of face / tongue / lip / throat / larynx / periorbital oedema)<br>Urticaria |
|  | Very rare | Hyperhidrosis<br>Swelling face  |
| Musculoskeletal and connective tissue disorders      | Uncommon  | Myalgia<br>Arthralgia   |
| General disorders and administration site conditions | Common    | Injection site reaction <sup>8</sup>  |
|  | Very rare | Injection site pain   |
|  | Not known | Injection site swelling<br>Malaise<br>Pyrexia   |

#### c) Description of selected adverse reactions:

- Hypersensitivity (anaphylactic or anaphylactoid reactions) may characteristically occur with various symptoms of rash (eruption), urticarial, pruritus, bronchospasm/asthma, wheezing, and angioedema. Angioedema include oedema of face / tongue / lip / throat / larynx / periorbital oedema. Laryngo-pharyngeal oedema may characteristically occur with hoarseness and / or dysphagia. Bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea;
- These neural pathologies may occur with the various symptoms of abnormal sensations of the lips, tongue, and oral tissues.
- Respiratory depression may characteristically occur with various symptoms such as apnoea (respiratory arrest);
- These neurally mediated effects are due to the presence of local anaesthetic / vasoconstrictor at excessive concentrations regionally or in the systemic circulation;
- This mostly occurs in patients with underlying cardiac disease or those receiving certain drugs (section 4.5)
- Necrosis is due to excessive local effect of the vasoconstrictor and mostly occurs in patients with underlying ischemic diseases;
- This may be the sign of an injury to the lingual nerve
- Procedural pain, post procedural pain and contusion are symptoms that may be associated to injection site reaction

Because of the presence of adrenaline, precautions and monitoring should be enhanced in the following situations: patients stressed prior dental procedure. Any previous knowledge of such underlying conditions in patients requiring dental anaesthesia should be minded and a minimal dose of local anaesthetic with vasoconstrictor used.

**d) Paediatric population:** The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults.

#### 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il/>

#### 4.9) Overdose:

##### • Types of overdose:

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

- Absolute overdose
- Relative overdose
  - inadvertent injection into a blood vessel, or
  - abnormal rapid absorption into the systemic circulation, or
  - delayed metabolism and elimination of the product.

##### • Symptomatology:

- Due to lidocaine: The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations, followed by vascular, respiratory, and finally cardiac toxicity (detailed in section 4.8).

- Due to adrenaline: Overdose of adrenaline may cause cardiovascular effects.

• **Treatment of overdose:**

The availability of resuscitation equipment should be ensured before the onset of dental anaesthesia with local anaesthetics.

If signs of acute toxicity are suspected, the injection of this product must immediately be stopped.

Oxygen should rapidly be administered, if necessary by assisted ventilation. Change patient position to supine position if necessary.

In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation is necessary.

**5) PHARMACOLOGICAL PROPERTIES**

**5.1) Pharmacodynamic properties:**

Pharmacotherapeutic group: Nervous System / Local Anaesthetics / Anaesthetics, local / Amides / Lidocaine, combinations

ATC Code: N01BB52

Mechanism of action: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anaesthetic action.

Since lidocaine, as most agents currently used for local anaesthesia, is not a vasoconstrictor, adrenaline is included in the solution with the anaesthetic:

- by localizing the solution at the site of the injection, this vasoconstrictor intensifies and prolongs the anaesthetic effect and decreases the rate at which the anaesthetic drug enters the systemic circulation,
- the presence of a vasoconstrictor also decreases surgical haemorrhage in the immediate area of injection.

Onset duration of anaesthesia:

- When used for infiltration anaesthesia in dental patients, the time of onset averages less than two minutes. XYLONOR EPINEPHRINE provides an average pulp anaesthesia of at least sixty minutes with an average duration of soft tissue anaesthesia of approximately two and a half hours.
- When used for nerve blocks in dental patients, the time of onset averages two to four minutes. XYLONOR EPINEPHRINE provides pulp anaesthesia averaging at least ninety minutes with an average duration of soft tissue anaesthesia of three to three and a quarter hours.
- Hemodynamics:
  - Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anaesthetic agent on various components of the cardiovascular system and/or the betaadrenergic receptor stimulating action of adrenaline when present.

**5.2) Pharmacokinetic properties:** Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administrations, its rate of absorption depending upon various factors, such as the site of administration, and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion. Approximately 90 % of lidocaine administered is excreted in the form of various metabolites, and less than 10 % is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per ml. In the rhesus monkey, arterial blood levels of 18-21 mcg/ml have been shown to be threshold for convulsive activity.

**5.3) Preclinical safety data:** Toxicity studies were performed with lidocaine, adrenaline and lidocaine with adrenaline. No teratogenic effects were observed with lidocaine. However, some effects on fertility and teratogenicity were observed in animals treated with adrenaline at doses much higher than those recommended for dental treatments in humans.

**6) PHARMACEUTICAL PARTICULARS**

**6.1) List of excipients:** Sodium Chloride, Potassium Metabisulfite (E224), Disodium Edetate, Sodium Hydroxide (for pH-adjustment) and Water for Injections.

**6.2) Incompatibilities:** None stated.

**6.3) Shelf life:** The expiry date of the product is indicated on the label and packaging. Do not use after the expiry date. Shelf life after first opening: refer to section 6.6.

**6.4) Special precautions for storage:** Store below 25°C. Keep the cartridges in the outer carton tightly closed, in order to protect from light. Do not freeze.

**6.5) Nature and contents of container:** Glass cartridges with rubber closures. 10, 20, 30, 40 or 50 dental cartridges of 1.7 ml in blister packs grouped in a cardboard box. Not all pack sizes may be marketed.

**6.6) Special precautions for disposal:** One cartridge can only be used for one single patient during one single session. No opened cartridge of an anaesthetic solution should be reused. If only a part is used, the remainder must be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

**7) Israeli drug registration number:** 154-82-34604-00

**8) Manufacturer:** Septodont, Saint-Maur-Des-Fossés, France.

**9) Israeli marketing authorization holder:** A. Levy Dental Co. Ltd., VAT # 510917768, 27 Kalisher Street, Tel Aviv 6516506, Israel.

**10) REVISED ON: 02/2021**

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