Xylestesin™-A

Solution for injection
(local anaesthetic for dentistry)

INFORMATION FOR USE

3M Deutschland GmbH
Carl-Schurz-Str. 1
41453 Neuss
Germany

COMPOSITION
1 ml solution for injection contains:
Active ingredients:

Anhydrous lidocaine hydrochloride (equivalent to 21 mg lidocaine hydrochloride monohydrate)	20 mg
Epinephrine (adrenaline) as epinephrine (adrenaline) hydrochloride	12.5 micrograms

Other ingredients:
Sodium sulphite (E221) 0.6 mg
Sodium chloride
Water for injections

PHARMACEUTICAL FORM AND CONTENT
Solution for injection, 50 cartridges of 1.7 ml each
Local anaesthetic of the anilide series with vasoconstrictive component for administration in dentistry

THERAPEUTIC INDICATIONS
Infiltration anaesthesia and nerve-block in dentistry.
Xylestesin-A is indicated in adults, children and adolescents.

CONTRAINDICATIONS
Xylestesin-A must not be used in the event of
- hypersensitivity to the active substances, sodium sulphite (E221) or to any of the other excipients.

Due to the active substance lidocaine, Xylestesin-A must not be used in the event of
- known allergy or hypersensitivity to local anaesthetics of the amide type,
- severe, uncontrolled or untreated excitation and conduction disorders of the heart (e.g. grade II and III AV block, pronounced bradycardia),
- acutely decompensated heart failure,
- severe hypotension.

Due to the content of epinephrine as a vasoconstrictor admixture, Xylestesin-A must not be used in the event of
- Heart diseases such as:
  - unstable angina pectoris,
  - recent myocardial infarction,
  - recent coronary artery bypass surgery,
  - refractory arrhythmias and paroxysmal tachycardia or high-frequency, continuous arrhythmia,
  - untreated or uncontrolled severe hypertension,
  - untreated or uncontrolled congestive heart failure,

– concomitant treatment, or treatment during the past 14 days with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (see section Interactions).
– Xylestesin-A must not be used in acra of extremities

Due to the content of sulphite as excipient, Xylestesin-A must not be used in the event of
- allergy or hypersensitivity to sulphite,
- severe bronchial asthma.

Xylestesin-A can provoke acute allergic reactions with anaphylactic symptoms (e.g. bronchospasm).

Precaution for use and Pregnancy/lactation see separate section

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special warnings

Xylestesin-A must be used with particular caution in the event of
– severely impaired renal or hepatic function,
– angina pectoris (see section Posology and method of administration and section Contraindications),
– arteriosclerosis,
– considerably impaired blood coagulation or concomitant treatment with anticoagulants or platelet aggregation inhibitors (e.g. heparin or acetylsalicylic acid). The overall risk of bleeding is increased.
– haemorrhagic diathesis – increased bleeding risk particularly with nerve-block anaesthesia
– uncontrolled or untreated hyperthyroidism,
– narrow-angle glaucoma,
– diabetes mellitus,
– lung diseases – particularly allergic bronchial asthma,
– phaeochromocytoma,
– methaemoglobinaemia
– impaired cardiovascular function due to decreased ability to compensate prolonged AV conduction,
– epilepsy (Avoid high doses!),
– blood screening tests on athletes as Xylestesin-A may show positive results. Lidocaine is not listed in the current WADA list. The listed epinephrine can be used in local anaesthetics.

This medicinal product contains less than 1 mmol (23 mg) sodium per 1.7 ml, i.e. essentially “sodium free”.
Sodium sulphite (E221): May rarely cause severe hypersensitivity reactions and bronchospasm.

Precautions for use:

- Information for patients: The patient should be advised to exert caution to avoid inadvertent trauma to the lips, tongue, cheek mucosae or soft palate while these structures are anaesthetized. The patient should therefore avoid eating until the anaesthetic has worn off.

- The lower blood flow in the pulp tissue due to the epinephrine content and thus the risk of overlooking an opened pulp has to be taken into account regarding cavity or crown preparations.

- Injection into an inflamed area should be avoided due to reduced penetration of lidocaine into an inflamed tissue.

- Dental practitioners who employ local anaesthetic agents should be well versed in diagnosis and management of emergencies which may arise from their use.

- Inadvertent intravascular application must be avoided (see section Posology and method of administration). Accidental intravascular injection or accidental overdose may be associated with convulsions, followed by central nervous system depression or cardiorespiratory arrest (see section Therapy of overdose).

- Each time a local anaesthetic is used the following medicinal products/therapy as well as an indwelling venous cannula set should be available:
  - Anticonvulsant medicines (benzodiazepines e.g. diazepam), myorelaxants, glucocorticoids, atropine and vasopressors or adrenaline as well as an electrolyte solution for a severe allergic or anaphylactic reaction.
  - Resuscitation equipment (in particular a source of oxygen) enabling artificial ventilation if necessary.

- Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anaesthetic injection. Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity (see section Therapy of overdose).

Effects on the ability to drive and use machines
In sensitive patients, injection of Xylestesin-A can lead to a transient impairment of responsiveness, e.g. when driving a vehicle. The physician must decide on an individual basis whether the patient may drive or operate machinery.

PREGNANCY, LACTATION AND FERTILITY

Pregnancy

For Xylestesin-A no clinical data on exposed pregnancies are available. Lidocaine animal studies do not indicate any directly or indirectly harmful effects with respect to reproductive toxicity at doses 6.6 times the human dose. Animal studies carried out with epinephrine have shown reproductive toxicity. The potential risk for humans is unknown.

Caution should be exercised when prescribing to pregnant women. Xylestesin-A should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Small quantities of lidocaine are excreted into the breast milk but no effects on breast-fed neonates are likely at therapeutic doses. It is not known whether adrenaline is excreted into the breast milk.
A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Xylestesin-A should be made taking into account the benefit of breast-feeding to the child and the benefit of Xylestesin-A therapy to the woman.
Therefore, nursing mothers should milk and discard the first mother's milk following anaesthesia with lidocaine.

Fertility

Animal studies with high doses of lidocaine or adrenaline showed an effect on fertility. At therapeutic doses of Xylestesin-A, however, no effects on male or female fertility are likely.

INTERACTIONS

Interactions affecting the use of this medicinal product:

- Contraindicated of concomitant use:
  Patients taking MAO inhibitors or tricyclic antidepressants
  The sympathomimetic effect of epinephrine can be intensified by the simultaneous intake of MAO inhibitors or tricyclic antidepressants (see section Contraindications).

- Concomitant use is not recommended in:
  Patients taking phenothiazines and butyrophenones
  Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided. In situations where concurrent therapy is necessary, careful patient monitoring is essential.

  Patients taking non-selective beta-blockers
  The concomitant administration of non-cardioselective ß-blockers can lead to an increase in blood pressure due to the epinephrine in Xylestesin-A

  Inhalational anaesthetics
  Certain inhalational anaesthetics, such as halothane, can sensitise the heart to catecholamines and therefore induce arrhythmias following administration of Xylestesin-A. The use of Xylestesin-A during or following treatment with general anaesthesia should be avoided, if possible.

  Patients taking vasopressor and ergot-type oxytocic drugs
  Lidocaine hydrochloride with epinephrine 1:80,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur.

- Precautions including dose adjustment
  Local anaesthetics
  Caution is advised if lidocaine with epinephrine is used concurrently with other local anaesthetics. The toxic effects of local anaesthetics are additive. A major cause of adverse reactions appears to be excessive plasma concentrations, which may be due to accidental intravasal administration, slow metabolic degradation or overdosing.

Interactions resulting in clinically relevant changes on the use of other medicinal products:

- Concomitant use is not recommended in:
  Patients taking oral antidiabetics
  Epinephrine can inhibit insulin release in the pancreas and thus diminish the effect of oral antidiabetics.

Paediatric population

No significant differences can be expected regarding drug interactions between the adult and paediatric populations with regard to drug interactions.

POSOLOGY AND METHOD OF ADMINISTRATION

Xylestesin-A is exclusively recommended for use in dentistry.

Posology

The smallest possible volume of solution which will lead to an effective anaesthesia should be used.

Adults:

The dosage should be determined on an individual basis, according to the technique used and particularities of the specific case.
In oral infiltration and/or mandibular block, initial dosages of 1.0 – 4.0 ml are usually sufficient.

Special populations:

Elderly population: Increased plasma levels of Xylestesin-A can occur in older patients due to diminished metabolic processes and reduced distribution volume. The risk of accumulation of Xylestesin-A is increased after repeated administration in particular.
Dosages should be reduced from adult recommendations, taking into consideration any cardiac or liver disease (see section Special warnings and precautions for use).

Patients with hepatic impairment: Lidocaine is metabolized in the liver. Lower doses of lidocaine may be required in patients with hepatic dysfunction, due to prolonged effects and systemic accumulation (see section Special warnings and precautions for use).

Patients with renal impairment: Lidocaine and its metabolites are mainly eliminated in urine. Lower doses of lidocaine may be required in patients with severe renal dysfunction, due to prolonged effects and systemic accumulation (see section Special warnings and precautions for use).

Other relevant special populations: The dose has to be similarly reduced in patients with certain pre-existing diseases (angina pectoris, arteriosclerosis, see section Contraindications and section Special warnings and precautions for use) and in patients concurrently taking medications known to interact with lidocaine and/or epinephrine (see section Special warnings and precautions for use and section Interactions).

Dose recommendation for special populations: A lower dosage range is thus recommended in all such cases (i.e. minimum volume of Xylestesin-A for sufficient anaesthetic effect).

Paediatric population:

Xylestesin-A is indicated in adults, children and adolescents. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully. The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child’s weight (in kilograms) x 1.33.

Dose recommendation for children and adolescents:

Body weight (kg)	**Recommended dosage**	
	lidocaine hydrochloride mg/child	solution for injection ml/child
20 - <30	5-20 mg	0.25 ml – 1 ml
30- <40	10-40 mg	0.5 ml – 2 ml
40 - <50		
50 - < 60	10 – 60 mg	0.5 ml – 3 ml
60 - < 70	20 – 80 mg	1 ml – 4 ml
70 - < 80		

Due to the fact that lidocaine diffuses rapidly into tissues and the bone density is lower in children than in adults, infiltration anaesthesiacan be used instead of conduction anaesthesia in the paediatric population.

Maximum Recommended Dosage:
Adults:
For healthy adults, the maximum dose of the active ingredient lidocaine hydrochloride with vasoconstrictor admixture is 7mg/kg body weight.
Example: The maximum dose for a 70 kg patient is 500 mg. However, due to the addition of epinephrine 1:80,000, a maximum administered quantity of 16 ml solution for injection or 9 cartridges (equivalent to 0.2 mg epinephrine, maximum dose) must not be exceeded.

Children:
The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 5 mg lidocaine hydrochloride/kg BW or 0.250 ml Xylestesin-A/kg BW.

Maximum recommended dosage of Xylestesin-A in children and adolescents:

Body weight (kg) (Corresponding paediatric age groups according to ± limits of growth tables)	**Maximum** allowed dose based on 5 mg/kg BW	
	Lidocaine hydrochloride mg/child	solution for injection ml/child
20 - <30	100	5
30- <40	150	7.5
40 - <50	200	10.0
50 - <60	250	12.5
60 - <70	300	15.0
70 - <80	350	16.0

Method of administration

Dental use

To avoid intravascular injection, aspiration control at least in two planes (rotation of the needle by 180°) must always be carefully undertaken, although a negative aspiration result does not safely rule out an unintentional and unnoticed intravascular injection.

The injection rate should not exceed 0.5 ml in 15 seconds, i.e. 1 cartridge per minute.

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 – after allowing an interval of at least 20 – 30 seconds.

Opened cartridges must not be used in other patients. Residues must be discarded.

THERAPY OF OVERDOSE

Acute emergencies from local anaesthetics are generally related to high plasma levels encountered during therapeutic use or unintended and rapid intravascular administration of local anaesthetics. Symptoms of overdose may appear either immediately, caused by accidental intravascular injection or abnormal absorption conditions, e.g. in inflamed or well-vascularised tissue, or later, caused by genuine overdose following an injection of an excessive quantity of anaesthetic solution, and manifest themselves as central nervous and/or vascular symptoms.

Symptoms probably caused by lidocaine:

Cardiovascular symptoms (SOC Cardiac disorders, Vascular disorders, Investigations): blood pressure decreased, bradycardia, cardiac arrest, conduction disorder.

Central nervous symptoms (SOC Psychiatric disorders, Nervous system disorders, Ear and labyrinth disorders, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, Investigations): anxiety, coma, confusional state, dizziness, dysgeusia, grand mal convulsions, muscle twitching, nausea, respiratory paralysis, respiratory rate increased, restlessness, somnolence, tinnitus, tremor, vomiting.

The most dangerous symptoms regarding the outcome of such an event are:
blood pressure decreased, cardiac arrest, conduction disorder, grand mal convulsions, respiratory paralysis, and somnolence/coma.

Symptoms probably caused by epinephrine (adrenaline):

Pressure symptoms (SOC Vascular disorders, Investigations): blood pressure systolic increased, blood pressure diastolic increased, venous pressure increased, pulmonary arterial pressure increased, hypotension.

Cardiac symptoms (SOC Cardiac disorders): bradycardia, tachycardia, arrhythmia (e.g. atrial tachycardia, atrioventricular block, ventricular tachycardia, premature ventricular contractions). These symptoms can result in life-threatening situations as well as pulmonary oedema, cardiac arrest, kidney failure, and metabolic acidosis.

Therapy

If symptoms of overdose arise the application of the local anaesthetic has to be stopped.

General basic measures:

Diagnostics (respiration, circulation, consciousness), resuscitation and/or maintenance of the vital functions (respiration and circulation), administration of oxygen, intravenous access.

Special measures:

Hypertension:	Elevation of the upper body, if necessary sublingual nifedipine.
Convulsions:	Protect patients from concomitant injuries, if necessary benzodiazepines (e.g. diazepam i.v.).
Hypotension:	Horizontal position, if necessary intravenous infusion of a physiological electrolyte solution, vasopressors (e.g. etilefrine i.v.).
Bradycardia:	Atropine iv.
Anaphylactic shock:	Contact emergency physician, in the meantime shock positioning, generous infusion of a physiological electrolyte solution, if necessary epinephrine .i.v., cortisone i.v.
Cardiovascular arrest:	Immediate cardiopulmonary resuscitation, contact emergency physician.

UNDESIRABLE EFFECTS

a) Summary of the safety profile:

The causality assessment in case of adverse events is difficult, as they may be due to the underlying dental disease, the dental procedure or the local anaesthetic and clear differentiation is not possible. The description of the safety profile of Xylestesin-A is based on data identified in published clinical studies and on the postmarketing surveillance data of the MAH.

In clinical studies, the most frequently observed adverse events were hypoaesthesia oral (74%), followed by drug ineffective (8.5%) as well as pain, procedural pain, toothache (0.35-1.26%). With the exception of oral hypoaesthesia, no nerve disturbances were observed in clinical studies, which may be explained by the low patient numbers. Postmarketing surveillance data confirm the pattern described in published clinical studies in general, but indicated a lower overall incidence of adverse events. However it has to be considered that spontaneous reporting systems do not allow incidence calculation.

The overall risk of nerve disturbances (e.g. hypoaesthesia, paraesthesia, taste disorders) is low according to the postmarketing experience. In the case of suspected hypersensitivity reactions, allergy testing is recommended including testing of the individual components of the medicinal product.

b) Tabulated summary of adverse reactions:
The tabulated summary is based on data from published controlled clinical studies (N = 1,990 patients) and completed by postmarketing surveillance data (acquired over a 5-years interval):

Very common (> 1/10)
Common(≥ 1/100, <1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

System organ class	
Infections and infestations	*Uncommon* Oral herpes
Immune system disorders	*Not known** anaphylactic reaction, anaphylactic shock, type I hypersensitivity
Psychiatric disorders	*Not known** confusional state
Nervous system disorders	*Uncommon* dizziness
	Rare headache, somnolence
	*Not known** facial palsy, paresis, syncope, dysarthria
Eye disorders	*Not known** accommodation disorder, blindness, diplopia, eye swelling, vision blurred, eyelid ptosis, mydriasis, ophthalmoplegia
Cardiac disorders	*Rare* palpitations
Vascular disorders	*Rare* haematoma
	*Not known** pallor
Respiratory, thoracic and mediastinal disorders	*Not known** bronchospasm, laryngeal oedema, respiratory failure, throat tightness, wheezing, dyspnoea, cough
Gastrointestinal disorders	*Very common* hypoaesthesia oral
	Uncommon toothache, nausea
	*Not known** tongue oedema, vomiting

Skin and subcutaneous tissue disorders	*Rare* haemorrhage subcutaneous
	*Not known** dermatitis bullous, dermatitis contact, hypoaesthesia facial, pruritus, rash, swelling face
General disorders and administration site conditions	*Common* drug ineffective, pain
	Uncommon injection site swelling, injection site haematoma
Investigations	*Not known** allergy test positive, heart rate increased, heart rate irregular
Injury, poisoning and procedural complications	*Uncommon* procedural pain, mouth injury

* data from postmarketing surveillance representing 5 years of observation

c) Description of selected adverse events:

Two types of adverse events are of special clinical interest, but these are not the most frequently reported adverse events. The presentation is based mainly on postmarketing surveillance data.

Nerve disturbances
Nerve disturbances in dentistry may have different reasons, caused by the underlying dental disease, by the dental procedure, but also by direct adverse events of dental local anaesthetics. With an observation frequency of one event per 10 millions of sold cartridges the risk of such disturbances is low. In the data compilation given above the most frequently reported nerve disturbance in clinical studies was oral hypoaesthesia (mainly lip numbness). It should be taken into account that the high number of cases of oral hypoaesthesia reported in clinical studies may reflect only an individually increased duration of action of Xylestesin-A. During postmarketing surveillance, cases of facial palsy, hypoaesthesia facial and various adverse events affecting the eye (e.g. diplopia, accommodation disturbances) were identified indicating possibly anaesthesia related nerve disturbances. All of these adverse events were reversible.

Hypersensitivity reactions
Hypersensitivity reactions were only rarely identified in the postmarketing surveillance (6.41 events per 10 million sold cartridges). Mostly the reactions were non-serious (4.56/10 millions sold cartridges), but life-threatening reactions cannot be fully excluded. The reactions included anaphylactic reactions/shock, skin reactions and respiratory symptoms.
In the case of suspected hypersensitivity reaction, allergy testing is recommended including testing of the individual components of the medicinal product.

d) Paediatric population
The observation during postmarketing surveillance does not reveal differences in the safety profile in children compared with that in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product.

STORAGE INFORMATION

Do not use the preparation after the expiry date.
Do not store above 25°C. Store in the original package in order to protect from light.

DATE OF REVISION OF THE TEXT

04/2017

Keep the medicine out of the sight and reach of children!