

1. Name of the medicinal product

THEMICAINE 20mg/ml Injection

2. Qualitative and quantitative composition

Each 1ml of solution contains 2.0% w/v of Lidocaine Hydrochloride B.P.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for Injection

4. Clinical particulars

4.1 Therapeutic indications

Lidocaine is a local anaesthetic of the amide group. The injectable form has a wide range of applications for nerve blockade. It can be used by percutaneous infiltration; to block a major nerve plexus such as the brachial; for epidural anaesthesia; for intravenous regional analgesia.

4.2 Posology and method of administration

Posology

The dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given. The maximum dose for healthy adults should not exceed 200mg.

Children and elderly or debilitated patients require smaller doses, commensurate with age and physical status.

4.3 Contraindications

Hypersensitivity to the active substance, to anaesthetics of the amide type or to any of the excipients listed in section 6.1.

Lidocaine is contraindicated in patients with:

- Complete heart block
- Hypovolaemia

4.4 Special warnings and precautions for use

Lidocaine should be administered by persons with resuscitative skills and equipment. Facilities for resuscitation should be available when administering local anaesthetics.

It should be used with caution in patients with myasthenia gravis, epilepsy, congestive heart failure, bradycardia or respiratory depression, including where agents are known to interact with Lidocaine either to increase its availability or additive effects e.g. phenytoin or prolong its elimination e.g. hepatic or end renal insufficiency where the metabolites of Lidocaine may accumulate.

Intramuscular Lidocaine may increase creatinine phosphokinase concentrations which can interfere with the diagnosis of acute myocardial infarction. Lidocaine has been shown to be porphyrinogenic in animals and should be avoided in persons suffering from porphyria.

The effect of Lidocaine may be reduced if it is injected into inflamed or infected areas.

Hypokalaemia, hypoxia and disorder of acid-base balance should be corrected before treatment with intravenous lidocaine begins.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of local anaesthetic drug used.

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia, and therefore epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.

Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by preloading the circulation with crystalloidal or colloidal solutions. Hypotension should be treated promptly.

Paracervical block can sometimes cause foetal bradycardia or tachycardia and careful monitoring of the foetal heart rate is necessary (see section 4.6).

Injections in the head and neck regions may be made inadvertently into an artery causing cerebral symptoms even at low doses.

Retrobulbar injections may rarely reach the cranial subarachnoid space, causing serious/severe reactions including cardiovascular collapse, apnoea, convulsions and temporary blindness.

Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular motor dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves.

The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to local anaesthetic. For this reason, as with all local anaesthetic, the lowest effective concentration and dose of local anaesthetic should be used.

Lidocaine Hydrochloride 2% w/v Solution for Injection is not recommended in subjects with a shallow anterior chamber or a history of acute narrow angle glaucoma

Use of Lidocaine Hydrochloride 2% w/v Solution for Injection in patients with shallow anterior chamber, a history of acute narrow angle glaucoma and/or insufficient pupil dilation can increase the risk of both iridocoele and floppy iris syndrome.

Paediatric population

Lidocaine Injection is not recommended for use in neonates. The optimum serum concentration of lidocaine required to avoid toxicity, such as convulsions and cardiac arrhythmias, in this age group is not known.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Lidocaine toxicity is enhanced, by the co-administration of cimetidine and propranolol requiring a reduction in the dosage of lidocaine. Both drugs decrease hepatic blood flow. Also, cimetidine depresses microsomal activity. Ranitidine produces a small reduction in Lidocaine clearance. Increase in serum levels of lidocaine may also occur with anti-viral agents (e.g. amprenavir, atazanavir, darunavir, lopinavir).

Hypokalaemia caused by diuretics may antagonize the action of lidocaine if administered concomitantly (see section 4.4).

Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics (e.g. anti-arrhythmics, such as mexiletine), since the systemic toxic effects are additive. Specific interaction studies with lidocaine and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised.

There may be an increased risk of ventricular arrhythmia in patients treated concurrently with antipsychotics which prolong or may prolong the QT interval (e.g. pimozide, sertindole, olanzapine, quetiapine, zotepine), prenylamine,

adrenaline (if accidentally injected intravenously)) or 5HT3 antagonists (e.g. tropisetron, dolasetron).

Concomitant use of quinupristin/dalfopristin may increase lidocaine levels with a subsequent increased risk of ventricular arrhythmias and therefore should be avoided.

There may be an increased risk of enhanced and prolonged neuromuscular blockade in patients treated concurrently with muscle relaxants (e.g. suxamethonium).

Cardiovascular collapse has been reported following the use of bupivacaine in patients on treatment with verapamil and timolol; Lidocaine is closely related to bupivacaine.

Dopamine and 5 hydroxytryptamine reduce the convulsant threshold to Lidocaine.

Narcotics are probably proconvulsants and this would support the evidence that Lidocaine reduces the seizure threshold to fentanyl in man.

Opioid-antiemetic combination sometimes used for sedation in children could reduce the convulsant threshold to Lidocaine and increase the CNS depressant effect.

While adrenaline when used in conjunction with Lidocaine might decrease vascular absorption, it greatly increase the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although animal studies have revealed no evidence of harm to the foetus, lidocaine should not be administered during early pregnancy unless the benefits are considered to outweigh the risks.

Lidocaine readily crosses the placental barrier after epidural or intravenous administration to the mother. The ratio of umbilical to maternal venous concentration is 0.5 to 0.6. The foetus appears to be capable of metabolising Lidocaine at term. The elimination half life in the newborn of the drug received in utero is about three hours, compared with 100 minutes in the adult. Elevated lidocaine levels may persist in the newborn for at least 48 hours after delivery. Foetal bradycardia or tachycardia (see section 4.4), neonatal bradycardia, hypotonia or respiratory depression may occur.

Breast-feeding

Small amounts of Lidocaine are secreted into breast milk and the possibility of an allergic reaction in the infant, albeit remote, should be borne in mind when using lidocaine in nursing mothers.

Fertility

No data available

4.7 Effects on ability to drive and use machines

Where major motor nerve block occurs e.g. Brachial plexus, epidural, spinal block. Where there is a loss of sensation resulting from nerve block to areas of muscle co-ordination or balance. Advice is that for general anaesthesia as sedative/hypnotic drugs are often used during nerve blockade.

4.8 Undesirable effects

In common with other local anaesthetics, adverse reactions to Lidocaine are rare and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/or the cardiovascular system (see also 4.9 Overdose).

The undesirable effects are defined using the following convention: Not known (cannot be estimated from the available data).

Blood and Lymphatic System Disorders

Lidocaine may also result in methaemoglobinaemia.

Immune system disorders

Hypersensitivity reactions (allergic or anaphylactoid reactions, anaphylactic shock) – see also Skin & subcutaneous tissue disorders).

Skin testing for allergy to Lidocaine is not considered to be reliable.

Nervous & Psychiatric disorders

Neurological signs of systemic toxicity include dizziness or light-headedness, nervousness, tremor, circumoral paraesthesia, tongue numbness, drowsiness, convulsions, coma.

Nervous system reactions may be excitatory and or depressant. Signs of CNS stimulation may be brief, or may not occur at all, so that the first signs of toxicity may be confusion and drowsiness, followed by coma and respiratory failure.

Neurological complications of spinal anaesthesia include transient neurological symptoms such as pain of the lower back, buttock and legs. These symptoms usually develop within twenty-four hours of anaesthesia and resolve within a few days. Isolated cases of arachnoiditis or cauda equina syndrome, with persistent paraesthesia, bowel and urinary dysfunction, or lower limb paralysis have been reported following spinal anaesthesia with lidocaine and other similar agents. The majority of cases have been associated with hyperbaric concentrations of Lidocaine or prolonged spinal infusion.

Eye disorders

Blurred vision, diplopia and transient amaurosis may be signs of lidocaine toxicity.

Bilateral amaurosis may also be a consequence of accidental injection of the optic nerve sheath during ocular procedures. Orbital inflammation and diplopia have been reported following retro or peribulbar anaesthesia (see section 4.4 Special warnings and precautions for use)

Ear and labyrinth disorders

Tinnitus, hyperacusis.

Cardiac and vascular disorders

Cardiovascular reactions are depressant and may manifest as hypotension, bradycardia, myocardial depression, cardiac arrhythmias and possibly cardiac arrest or circulatory collapse.

Hypotension may accompany spinal and epidural anesthesia. Isolated cases of bradycardia and cardiac arrest have also been reported.

Respiratory, thoracic or mediastinal disorders

Dyspnoea, bronchospasm, respiratory depression, respiratory arrest.

Gastrointestinal disorders

Nausea, vomiting.

Skin & subcutaneous tissue disorders

Rash, urticaria, angioedema, face oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to

report any suspected adverse reactions to the Pharmacy and Poisons Board (PPB) through the Pharmacovigilance Electronic Reporting System (PvERS) at <https://pv.pharmacyboardkenya.org/> or by using the approved PPB ADR reporting forms

4.9 Overdose

Symptoms of acute systemic toxicity

Central nervous system toxicity presents with symptoms of increasing severity. Patients may present initially with circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome.

Recovery occurs as a consequence of redistribution of the local anaesthetic drug from the central nervous system and metabolism and may be rapid unless large amounts of the drug have been injected.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, injection of the anaesthetic should be stopped immediately.

Treatment will be required if convulsions and CNS depression occurs. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. A patent airway should be established and oxygen should be administered, together with assisted ventilation (mask and bag) if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor agent may be considered although this involves a risk of CNS excitation. Convulsions may be controlled by the intravenous administration of Diazepam or Thiopentone Sodium, bearing in mind that anti-convulsant drugs may also depress respiration and the

circulation. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation and early endotracheal intubation should be considered. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted. Continual optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides, ATC code: N01BB02

Mechanism of action

Lidocaine is used to provide anaesthesia by nerve blockade at various sites in the body and in the control of dysrhythmias. It has a rapid onset of action (about one minute following intravenous injection and fifteen minutes following intramuscular injection) and rapidly spreads through the surrounding tissues. The effect lasts about ten to twenty minutes and about sixty to ninety minutes following intravenous and intramuscular injection respectively.

5.2 Pharmacokinetic properties

The concentration of Lidocaine in the blood will be determined by its rate of absorption from the site of injection, the rate of tissue distribution and the rate of metabolism and excretion.

Absorption

The systemic absorption of Lidocaine is determined by the site of injection, the dosage and its pharmacological profile. The maximum blood concentration occurs following intercostal nerve blockade followed in order of decreasing concentration, the lumbar epidural space, brachial plexus site and subcutaneous tissue. The total dose injected regardless of the site is the primary determinant of the absorption rate and blood levels achieved. There is a linear relationship between the amount of Lidocaine injected and the resultant peak anaesthetic blood levels.

The lipid solubility and vasodilator activity will also influence its rate of absorption. This is seen in the epidural space where Lidocaine is absorbed more rapidly than prilocaine.

Distribution

Lidocaine is distributed throughout the total body water. Its rate of disappearance from the blood can be described by a two or three compartment model. There is a rapid disappearance (alpha) phase which is believed to be related to uptake by rapidly equilibrating tissues (i.e. tissues with a high vascular perfusion). The slower phase is related to distribution, to slowly equilibrating tissues (Betaphase) and to its metabolism and excretion (Gamma phase).

Lidocaine is distributed less rapidly than prilocaine (an amide drug of similar potency and duration of action) but equally as with mepivacaine. Its distribution is throughout all body tissues. In general, the more highly perfused organs will show higher concentrations of Lidocaine. The highest percentage of this drug will be found in skeletal muscle. This is because of the mass of muscle rather than an affinity.

Biotransformation

Lidocaine undergoes enzymatic degradation primarily in the liver. Some degradation may take in tissues other than liver. The main pathway involves oxidative de-ethylation to monoethylglycinexylidide followed by a subsequent hydrolysis to xylidine.

Elimination

The excretion occurs via the kidney with less than 5% in the unchanged form appearing in the urine. The renal clearance is inversely related to its protein binding affinity and the pH of the urine. This suggests by the latter that excretion of Lidocaine occurs by non-ionic diffusion.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

6.2 Incompatibilities

Lidocaine has been found to be incompatible when mixed with amphotericin, methohexitone and glyceryl trinitrate. It is not advisable to mix Lidocaine with other agents.

6.3 Shelf life

24 months

If only part of an ampoule is used, the remainder should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.

Keep in outer carton.

6.5 Nature and contents of container

Themicaïne is packed in 30 ml amber colour glass vial USP Type - I with bromo butyl rubber plug and blue colour aluminium flip of seal. 1 such vial packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

For Percutaneous infiltration, Epidural or IV use.

Use as directed by the physician.

Keep out of the sight and reach of children.

If only part used, discard the remaining solution.

7. Marketing authorisation holder

Themis Medicare Ltd

8. Marketing authorisation number(s)

H2025/CTD11214/21479

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text