1.4	**Product information**

1.4.1	**Prescribing Information (Summary of Product characteristics)-** Attached

1. NAME OF THE MEDICINAL PRODUCT

LIDOCAINE HYDROCHLORIDE INJECTION USP 20MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Lidocaine Hydrochloride USP

Eq. to anhydrous Lidocaine Hydrochloride 20 mg

Methyl Paraben NF 1 mg

(As preservative)

3. PHARMACEUTICAL FORM

Liquid Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Intravenous regional anaesthesia, infiltration anaesthesia, nerve blocks and epidural anaesthesia. Lidocaine Amneal 20 mg/ml is intended for adults.

4.2 Posology and Method of Administration

Posology

Lidocaine Amneal should only be used by, or under the supervision of, doctors with experience of regional anaesthesia and resuscitative skills. Facilities for resuscitation should be available when administering local anaesthetics. The lowest possible dose producing the required effect should be given.

The table may serve as a guide for adults having a body weight of about 70 kilograms. The dose should be adjusted according to age, weight and condition of the patient.

Route of administration or procedure	Recommended doses of Lidocaine hydrochloride		
	Concentration (mg/ml)	Volume (ml)	Total dose (mg)
Infiltration anaesthesia:			
Small procedures	10 mg/ml	2-10 ml	20-100 mg
Large procedures	10 mg/ml 20 mg/ml	10-20 ml 5-10 ml	100-200 mg 100-200 mg
Intravenous regional anaesthesia:			
Arm	10 mg/ml 20 mg/ml	10-20 ml 5-10 ml	100-200 mg 100-200 mg
Leg	10 mg/ml 20 mg/ml	20 ml 10 ml	200 mg 200 mg
Nerve blocks	10 mg/ml 20 mg/ml	2-20 ml 1-10 ml	20-200 mg 20-200 mg
Epidural anaesthesia:			
Lumbar analgesia	10 mg/ml 20 mg/ml	25-40 ml 12.5-20 ml	250-400 mg 250-400 mg
Thoracic anaesthesia	10 mg/ml 20 mg/ml	20-30 ml 10-15 ml	200-300 mg 200-300 mg
Sacral surgery analgesia	10 mg/ml	40 ml	400 mg
	20 mg/ml	20 ml	400 mg
Sacral obstetric analgesia	10 mg/ml 20 mg/ml	20-30 ml 10-15 ml	200-300 mg 200-300 mg

The recommended maximum single dose of lidocaine hydrochloride should not exceed 400 mg.

Paediatric population

The doses are reduced to children and patients with poor general condition.

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.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

Lidocaine Injection is not recommended for use in neonates (see section 5.2). The optimum serum concentration of lidocaine required to avoid toxicity, such as convulsions and cardiac arrhythmias, in this age group is not known.

Special population

The doses should be reduced in patients with renal impairment, hepatic impairment and the elderly, commensurate with age and physical status (see section 4.4).

Method of administration

The method of administration of lidocaine varies according to the procedure.

Lidocaine may be administered by intravenous, intramuscular, subcutaneous or epidural injection.

4.3 Contraindications:

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

Lidocaine should not be used for epidural anaesthesia in patients with pronounced hypotension or with cardiogenic or hypovolemic shock.

4.4 Special warnings and precautions for use:

With the exception of the most trivial procedures, regional and local anaesthetic procedures should always be carried out with equipment for resuscitation available. In any large blockade an intravenous cannula should be inserted before the local anaesthetic is injected. As with all local anaesthetic agents, lidocaine can cause acute central nervous and cardiovascular toxic effects when its use causes high concentrations in the blood, particularly after extensive intravascular administration.

Caution should be exercised in the treatment of the following patient categories:

- The elderly and generally debilitated patients.
- Patients with AV block II or III, as local anaesthetic can decrease myocardial conductivity.
- Patients with congestive heart failure, bradycardia or impaired respiratory function.
- Patients with severe hepatic disease or renal impairment.
- Patients with epilepsy.
- patients with coagulopathy. Treatment with anticoagulants (eg. Heparin), NSAIDs or plasma substitutes causes increased bleeding tendency. Accidental injury of blood vessels may lead to serious bleedings. If necessary bleeding time and activated partial thromboplastin (aPTT), quicktest and platelet count should be checked.
- third trimester of pregnancy (see section 4.6)

Patients treated with class III antiarrhythmics (e.g. amiodarone) should be kept under careful supervision and ECG monitoring should be considered, as the cardiac effects of lidocaine and class III antiarrhythmics may be additive (see section 4.5).

There have been post-marketing reports of chondrolysis in patients receiving post- operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the

scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for lidocaine.

Epidural anaesthesia may cause severe side effects such as cardiovascular depression, especially in cases of concomitant hypovolaemia. Caution should always be exercised in patients with reduced cardiovascular function.

The main reasons are traumatic nerve injuries and/or local toxic effects on muscles and nerves caused by the injected local anaesthetic. Traumatic nerve injuries and/or local toxic effects on muscles and nerves are mainly caused by the injection of local anaesthetics. The extent of these tissue injuries depends on the size of the trauma, the concentration of the local anaesthetic and the duration of tissue exposure to the local anaesthetic. For this reason, the lowest effective dose should be used.

Accidental intravascular injections in the head and neck areas may cause 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 effect of local anaesthetics may be reduced if the injection is made into an inflamed or infected area.

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 not be administered to patients with acute porphyria, unless absolutely unavoidable. Strict caution should be exercised in all patients with porphyria.

Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by intravenous administration of crystalloidal or colloidal solutions.

Hypotension should be treated immediately, with, for example, ephedrine 5-10 mg intravenously, repeated as needed.

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

Lidocaine Amneal 10 mg/ml injectable solution contains 1.2 mmol (28 mg) of sodium per ampoule which should be considered during treatment of patients with low sodium diets.

Lidocaine Amneal 20 mg/ml injectable solution contains less than 1 mmol (23 mg) of sodium per ampoule, whereby it is considered essentially "sodium-free".

Paediatric population

Lidocaine solution for 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.

Lidocaine solution for injection is not approved for intrathecal administration (subarachnoidal anaesthesia). After intrathecal administration of lidocaine and other comparable drugs cauda equina-syndrome with persistent paraesthesia, gastro- intestinal and urinary tract dysfunction, or

paralysis of the lower extremities may occur. Most of these cases are associated with hyperbaric lidocaine concentrations or prolonged intrathecal infusion.

4.5 Interaction with other Medicinal products and other forms of Interaction

Drugs which inhibit the metabolism of lidocaine (e.g. cimetidine) may cause potentially toxic plasma concentrations when lidocaine is given repeatedly in high doses over long periods of time. Such interactions have no clinical relevance during short-term treatment with lidocaine in recommended doses.

Lidocaine should be used with caution in patients receiving other local anaesthetics or class Ib antiarrhythmic drugs, as the 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

4.6 Pregnancy and Lactation

Fertility

There are no human data regarding potential effects of lidocaine on fertility.

Pregnancy

There are no adequate data on treatment in pregnant women.

Lidocaine crosses the placenta (see section 5.2). It is reasonable to assume that lidocaine has been used in a great number of pregnant women and women of fertile age. There is no evidence that lidocaine causes disturbances in the reproductive process such as increased incidence of malformations. The risk to humans has, however, not been completely investigated.

Animal studies have shown reproductive toxicity (see section 5.3).

In short term use during pregnancy and at delivery the benefits should be weighed against the risks. Paracervical blockade or pudendal blockade with lidocaine increases the risk of reactions such as bradycardia/tachycardia in the foetus. The heart rate of the foetus must therefore be carefully monitored (see section 5.2).

Breast-feeding

Lidocaine is excreted in breast milk in small quantities. An effect on the child is unlikely when used at recommended doses. Breast feeding can therefore be continued during treatment with Lidocaine Amneal.

4.7 Effects on Ability to Drive and Use Machines:

Depending on dose and method of administration, lidocaine can have a temporary effect on movement and coordination, influencing the ability to drive and use machines. Patients should be advised to avoid these activities until normal function is fully restored.

4.8 Undesirable Effects

Undesirable effects caused by the medicine itself can be difficult to distinguish from the physiological effects of the nerve blockade (e.g. hypotension, bradycardia), and conditions caused by the needle directly (e.g. nerve injury) or indirectly (e.g. epidural abscess).

Very common (≥1/10)	*Vascular disorders*	Hypotension
	Gastrointestinal disorders	Nausea
Common (≥1/100 to <1/10)	*Nervous system disorders*	Paraesthesia, dizziness
	Cardiac disorders	Bradycardia
	Vascular disorders	Hypertension
	Gastrointestinal disorders	Vomiting
Uncommon (≥1/1,000 to <1/100)	*Nervous system disorders*	Symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, drowsiness, light-headedness, tinnitus, feeling of intoxication, dysarthria)
Rare (≥1/10,000 to <1/1,000)	*Immune system disorders*	Hypersensitivity reactions, urticaria, rash, angioedema, in severe cases anaphylactic shock
	Nervous system disorders	Neuropathy, peripheral nerve injuries, arachnoiditis
	Eye disorders	Double vision
	Cardiac disorders	Cardiac arrest, arrhythmias
	Respiratory, thoracic and mediastinal disorders	Respiratory depression

4.9 Overdose

Accidental intravascular injections of local anaesthetics can cause immediate systemic toxicity (within seconds to a few minutes). Signs of systemic toxicity due to overdose appear later (15-60 minutes after injection) as a result of a slower increase in the concentration of the local anaesthetic in the blood (see section 4.8). If signs of systemic toxicity appear, injection should be stopped immediately.

Toxicity:

Peroral administration: less than 50 mg seems to be of no risk for young children. 75 mg to a 2-year old child reduced the pain, 100 mg to 5 months child gave severe, 300 + 300 mg within 4 hours to 3½-year old child gave severe to very severe, 400- 500 mg to 2-year old child and 1 g for 12 hours to a 1-year old child gave very severe intoxication. 600 mg to an adult reduced the pain, 2 g to an adult gave moderate intoxication.

Parenteral administration: 50 mg i.v. to a child of 1 month gave very severe intoxication. 200-400 mg infiltration to an adult gave severe, 500 mg to an elderly of 80-years old and 1 g i.v. to adults gave very severe intoxication.
Topical administration: 8.6-17.2 mg/kg to young children when application on burn wounds of the skin gave severe intoxication.
Symptoms
First CNS excitation, subsequently CNS depression. In large doses, rapid onset of convulsions can be the first symptom. Restlessness, dizziness, visual disturbances, perioral paraesthesia, nausea. Subsequently ataxia, auditory changes, euphoria, confusion, speech difficulty, paleness, sweating, tremor, convulsions, coma, respiratory arrest. Arrhythmias, mainly bradyarrhythmias, but with large doses, also ventricular tachycardia, ventricular fibrillation, QRS widening, AV block. Heart failure, hypotension (methemoglobinaemia described in isolated cases).
Treatment
Activated charcoal at peroral overdosage. (Provoked vomiting may be dangerous due to mucosal anaesthesia and risk for convulsions in an early stage. If a gastric lavage is necessary, it should be performed via a tube and after endotracheal intubation).
In the event of an overdose, immediate steps should be taken to maintain the circulation and respiration and to control convulsions.
A patent airway should be established and oxygen should be administered, together with assisted ventilation if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids, dobutamine and, if necessary, noradrenaline (initially 0.05 µg/kg/min, increasing as needed by 0.05 µg/kg/min every 10 minutes), with hemodynamic monitoring in more severe cases. Ephedrine can also be used.
Convulsions may be controlled by the intravenous administration of diazepam or thiopental sodium, bearing in mind that anticonvulsant drugs may also depress respiration and the circulation. Atropine may be given for bradycardia. If cardiac arrest should occur, standard resuscitation procedures should be instituted.
Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Local anaesthetics, amides,
ATC code: N01BB02
Lidocaine is a local anaesthetic of the amide type. The mechanism of action is based on a decreased permeability of the membrane of the neuron for sodium ions. As a consequence of this, the depolarization rate is decreased and the threshold of excitation is increased, resulting in a reversible local numbness.
It is used to provide local anaesthesia by nerve blockade at various sites in the body and in the control of dysrhythmias. It acts by inhibiting the ionic refluxes required for the initiation and conduction of impulses, thereby stabilising the neuronal membrane. In addition to blocking conduction in nerve axons in the peripheral nervous system, lidocaine has important effects on the

central nervous system and cardiovascular system. After absorption, lidocaine may cause stimulation of the CNS followed by depression and in the cardiovascular system, it acts primarily on the myocardium where it may produce decreases in electrical excitability, conduction rate and force of contraction. 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

Absorption

Lidocaine is absorbed rapidly from the gastro-intestinal canal but only low amounts reached the circulation due to the first-pass effect in the liver.

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 rate of absorption will depend on dose, route of administration and perfusion at the injection site. Intercostal blockades lead to the highest plasma concentrations (approx. 1.5 µg/ml per 100 mg injected), whereas subcutaneous injections in the abdominal area lead to lowest plasma concentrations (approx. 0.5 µg/ml per 100 mg injected). The volume of distribution at steady state is 91 litres and binding to plasma proteins, mainly to alpha-1-acid glycoprotein, is 65 %.

Absorption is total and biphasic from the epidural space with half-lives of approximately 9.3 minutes and 82 minutes respectively. The slow absorption is the time-limiting factor in elimination of lidocaine, which explains the slower elimination after epidural injection than after intravenous injection.

Elimination

Elimination of lidocaine is chiefly through metabolism, mainly by dealkylation to monoethylglycine xylidide (MEGX). MEGX appears to occur in plasma concentrations similar to the parent substance.

The speed of elimination of lidocaine and MEGX after an intravenous bolus dose is approximately 1.5-2 hours and 2.5 hours respectively.

Due to rapid metabolism in the liver, the kinetics are sensitive to all hepatic conditions. The half-life can be more than doubled in patients with hepatic impairment. Renal impairment does not affect the kinetics but can increase the accumulation of metabolites.

Lidocaine crosses the placental barrier and concentration of unbound lidocaine will be the same in both mother and foetus. However, total plasma concentration will be lower in the foetus, due to a lower degree of protein binding.

Distribution

Lidocaine is bound to plasma proteins, including α1-acid glycoprotein (AAG) and albumin. The extent of binding is variable but is about 66%. The AAG plasma levels is low in neonates and the free biologically active lidocaine fraction is relatively high in neonates.
The drug crosses the blood-brain and placental barriers probably as a result of passive diffusion.
The plasma protein binding of lidocaine is dependent on the concentration of α1-acid glycoprotein. An increase of α1-acid glycoprotein due to several medical conditions (like trauma, MI, cancer etc.) may affect distribution of lidocaine.
Special population groups
Hepatic impairment
The pharmacokinetics of lidocaine can be influenced by conditions affecting the liver function due to its rapid metabolism. The half-life can be increased by a factor of 2 or more in patients with hepatic dysfunction.
Renal impairment
Renal function impairment has no effect on the pharmacokinetics of lidocaine but may lead to the accumulation of its metabolites.
Paediatric population
In neonates, the α1-acid glycoprotein levels are low and protein binding may be reduced. As the free fraction may be higher, the use of lidocaine in neonates is not recommended.
Elderly
Elimination half-life and volume of distribution may appear to be prolonged resp. increased in the elderly due to reduced cardiac output and/or hepatic blood flow.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

Shelf-life of the medicinal product as packaged for sale: 36 months.

6.2 Special Precautions for Storage

Store below 300C.Protect from light.

6.3 Nature and Contents of Container

20ml USP Type I Amber coloured glass vial

6.4 Special Precautions for Disposal and Other Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
This medicine is for single use only.
If only part of an ampoule is used, discard the remaining solution.
The solution should be visually inspected before use. Use only if solution is clear and free from visible particles.

7. MARKETING AUTHORISATION HOLDER

CIRON DRUGS & PHARMACEUTICALS PVT. LTD.
C-1101/1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway,
Goregaon (East), Mumbai -400063
Tel N0- +91-22-33598000
E Mail: mail@cironpharma.com
Website: www.cironpharma.com

8. MARKETING AUTHORISATION NUMBER(S)

None