1 LIDOCAINE-BAXTER (solution for infusion)

Lidocaine-Baxter 1% w/v solution for injection.
Lidocaine-Baxter 2% w/v solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Lidocaine-Baxter 1% w/v: Lidocaine hydrochloride monohydrate 10.66mg/mL (= Lidocaine hydrochloride 10.0mg/mL).
Lidocaine-Baxter 2% w/v: Lidocaine hydrochloride monohydrate 21.32mg/mL (= Lidocaine hydrochloride 20.0mg/mL).

Note: Lidocaine is another name for lignocaine. Lidocaine is mostly used in this document.For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Appearance

Lidocaine-Baxter is a clear, colourless, particle-free, sterile, isotonic, pH adjusted solution of Lidocaine hydrochloride Ph Eur conforming to Lidocaine Injection BP.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine solutions are indicated for the production of local or regional anaesthesia by the following techniques: local infiltration; minor or major nerve blocks; epidural block; arthroscopy; intravenous regional anaesthesia.

4.2 Dose and method of administration

Adults and children above 12 years

The following table is a guide to dosage for the more commonly used techniques in the average adult. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. The lowest dose required for adequate anaesthesia should be used (see section 4.4). Individual variations in onset and duration occur.

Table 1 Dosage recommendations

Type of block	Concentration (mg/mL)	Dose		Onset (min)	Duration of effect (h)
		(mL)	(mg)		
SURGICAL ANAESTHESIA					
Lumbar epidural administration [1]	20	15 to 25	300 to 500	15 to 20	1.5 to 2
Thoracic epidural administration [1]	15	10 to 15	150 to 225	10 to 20	1 to 1.5
	20	10 to 15	200 to 300	10 to 20	1.5 to 2
Caudal epidural block [1]	10	20 to 30	200 to 300	15 to 30	1 to 1.5
	20	15 to 25	300 to 500	15 to 30	1.5 to 2

Table 1 Dosage recommendations					
Type of block	**Concentration (mg/mL)**	**Dose**		**Onset (min)**	**Duration of effect (h)**
		(mL)	**(mg)**		
IV regional (Bier´s block)					
a) Upper limb [2]	5	40	200	10 to 15	until tourniquet release
b) Lower limb [2]					until tourniquet release
i. thigh tourniquet	5	60	300	10 to 15	
ii.calf tourniquet	5	40	200	10 to 15	
Intra-articular block [3]	5	≤ 60	≤ 300	5 to 10	30 to 60 minutes after washout
	10	≤ 40	≤ 400	5 to 10	
FIELD BLOCK (e.g. minor nerve blocks and infiltration)					
Infiltration	5	≤ 80	≤ 400	1 to 2	1.5 to 2
	10	≤ 40	≤ 400	1 to 2	2 to 3
Digital block	10	1 to 5	10 to 50	2 to 5	1.5 to 2
Intercostals (per nerve) [Maximal number of nerves blocked at same time should be ≤ 8]	10	2 to 5	20 to 50	3 to 5	1 to 2
	15	2 to 4	30 to 60	3 to 5	2 to 3
Retrobulbar	20	4	80	1.5 to 2	1.5 to 2
Peribulbar	10	10 to 15	100 to 150	1.5 to 2	1.5 to 2
Pudendal (each side)	10	10	100	5 to 10	1.5 to 2
MAJOR NERVE BLOCK					
Paracervical (each side)	10	10	100	3 to 5	1 to 1.5
Brachial plexus: axillary	10	40 to 50	400 to 500	15 to 30	1.5 to 2
	15	30 to 50	450 to 600	15 to 30	1.5 to 3
Supraclavicular, Interscalene and subclavian perivascular	10	30 to 40	300 to 400	15 to 30	1.5 to 2
	15	20 to 30	300 to 450	15 to 30	1.5 to 3
Sciatic	15	15 to 20	225 to 300	15 to 30	2 to 3
	20	15 to 20	300 to 400	15 to 30	2 to 3
3 in 1 (femoral, obturator and lateral cutaneous)	10	30 to 40	300 to 400	15 to 30	1.5 to 2
	15	30	450	15 to 30	2 to 3

Remarks:

1) Dose includes test dose
2) Do not deflate tourniquet within 20 min of injection
3) There have been post marketing reports of chondrolysis in patients receiving post- operative intra-articular continuous infusion of local anaesthetics. Lidocaine is not approved for this indication (see section 4.4).

≤ = up to.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of the higher concentrations and doses. When a less intense block is required, the use of a lower concentration is indicated. The volume of medicine used will affect the extent and spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected *slowly* or in incremental doses, at a rate of 100 to 200mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3 to 5mL short-acting local anaesthetic, containing adrenaline is recommended. An inadvertent intravascular injection may be recognized by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

Table 2 Dosage recommendations in children aged 1 to 12 years old

Type of block	Concentration (mg/mL)	Volume (mL/kg)	Dose (mg/kg)	Onset (min)	Duration (h)
Caudal epidural	10	0.5	5	10 to 15	1 to 1.5

Consider both age and weight for calculation of dosages.

The doses in Table 2 should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

4.3 Contraindications

- Known hypersensitivity to local anaesthetics of the amide type
- Known hypersensitivity to any of the excipients.
- Hypovolaemia.

4.4 Special warnings and precautions for use

General

Lidocaine should be administered by persons with resuscitative skills and equipment. Equipment and medicines necessary for monitoring and emergency resuscitation must be immediately available. When performing major blocks or using large doses, an IV cannula should be inserted before the local anaesthetic is injected. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see 4.9).

Lidocaine 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.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

- The elderly and patients in poor general condition.
- Patients with partial or complete heart block. – due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with advanced liver disease or severe renal dysfunction.

- Patients being treated with anti-arrhythmic drugs class III (eg. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see section 4.5).
- Patients with acute porphyria. Lidocaine is probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.
- There have been post-marketing reports of chondrolysis in patients receiving postoperative 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.

Intramuscular lidocaine may increase creatinine phosphokinase concentrations which can interfere with the diagnosis of acute myocardial infarction.

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.

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.

Dosage reduction may be required in patients presenting impaired hepatic function, cardiac failure or during prolonged administration to patients with renal failure.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of local anaesthetic used, for example:

- 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.
- Retrobulbar injections may occasionally reach the cranial subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle 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 anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated

- Injections in the head and neck regions may be made inadvertently into an artery causing cerebral symptoms even at low doses.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia and careful monitoring of the foetal heart rate is necessary (see section 4.6).

Epidural anaesthesia may lead to hypotension and bradycardia. This risk of such effects can be reduced e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathiomimetric intravenous, repeated as necessary.

Local anaesthetic solutions containing antimicrobial preservatives, should not be used for intrathecal anaesthesia.

4.5 Interaction with other medicines 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 microsomial activity. Ranitidine produces a small reduction in lidocaine clearance. Potentially toxic plasma concentrations may occur when lidocaine is given in repeated high doses over a long time period. However, such interactions should be of no clinical importance following short term treatment with lidocaine at recommended doses. 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 (refer to 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. certain anti-arrhythmics, such as mexiletine and tocainide, since the systemic toxic effects are additive. Specific interaction studies with lidocaine and class III antiarrhythmic medicines (e.g. amiodarone) have not been performed, but caution should be advised (see section 4.4).

Medicines that reduce the clearance of lidocaine (e.g. cimetidine or beta-blockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period. Such interactions should be of no clinical importance following short term treatment with lidocaine at recommended doses.

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 accidently 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 structurally 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 increases the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.

4.6 Fertility, pregnancy and lactation

Fertility

No fertility data are available.

Pregnancy (Category A)

Category A refers to medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

It is reasonable to assume that a large number of pregnant women and women of child- bearing age have been given lidocaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations.

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 new-born of the drug received *in utero* is about three hours, compared with 100 minutes in the adult. Elevated lidocaine levels may persist in the new-born for at least 48 hours after delivery. Foetal bradycardia or tachy-cardia, neonatal bradycardia, hypotonia or respiratory depression may occur. Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus.

Breast feeding

Lidocaine may enter into breast milk, but in such small amounts that there is generally no risk of this affecting the neonate.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile of lidocaine is similar to those of other amide local anaesthetics. Adverse reactions caused by lidocaine *per se* are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture.

Adverse reactions that are usually dose related include nervousness, blurred vision, dizziness, bradycardia, hypotension, tremor, nausea, vomiting, drowsiness, speech disturbances, perioral numbness, muscle twitching, confusion, vertigo or tinnitus, psychosis, seizures and respiratory depression. Others include metallic taste, rash, sinus arrest, atrioventricular block, urticaria and anaphylactoid reactions.

Table of adverse drug reactions

Common (> 1/100 < 1/10)

Vascular disorders: hypotension, hypertension.

Gastrointestinal disorders: nausea, vomiting.

Nervous system disorders: paraesthesia, dizziness.

Cardiac disorders: bradycardia.

Uncommon (> 1/1,000 < 1/100)

Nervous system disorders: signs and symptoms of CNS toxicity (convulsions, paraesthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, tremor, tinnitus, dysarthria, CNS depression).

Rare (< 1/1,000)

Cardiac disorders: cardiac arrest, cardiac arrhythmias.

Immune system disorders: allergic reactions, anaphylactic reaction/shock.

Respiratory disorders: respiratory depression.

Nervous system disorders: neuropathy, peripheral nerve injury, arachnoiditis.

Eye disorders: diplopia.

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.9). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the medication, both quantitatively and qualitatively. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with medications such as benzodiazepine or barbiturate.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually, circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for a neurotic behaviour. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the local anaesthetic have been injected.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must be promptly treated with appropriate airway/respiratory support and the administration of anticonvulsant medicines.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, chronotropic and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphv.otago.ac.nz/reporting/

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 to 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

Signs and symptoms

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

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.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code

N01BB02: nervous system, anesthetics, anesthetics/local, amides.

Actions

Lidocaine is used to provide anaesthesia by reversible 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. With a medium duration of action, the effect lasts about ten to twenty minutes and about sixty to ninety minutes following intravenous and intramuscular injection respectively.

The 2% solution will last 1½ - 2h when given epidurally, and up to 5 hours with peripheral nerve blocks. When used in concentrations of 1%, there is less effect on motor nerve fibres and the duration of action is shorter.

Onset and the duration of the local anaesthetic effect of lidocaine depends on the dose and the site of administration.

Lidocaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres. The sodium channels of the nerve membrane are considered a receptor for local anaesthetic molecules.

Local anaesthetics may have similar effects on other excitable membranes e.g. brain and myocardium. If excessive amounts of medicine reach the systemic circulation, symptoms and signs of toxicity may appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity (see section 4.9) usually precedes the cardiovascular effects, as central nervous system toxicity occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

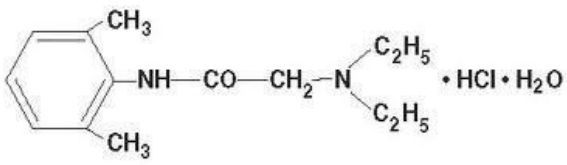
Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural administration depending on the extent of the concomitant sympathetic block.

5.2 Pharmacokinetic properties

Chemical name of lignocaine hydrochloride is 2-(diethylamino)-N-(2,6- dimethylphenyl) acetamide hydrochloride monohydrate.

The empirical formula is $C_{14}H_{22}N_2O \bullet HCl \bullet H_2O$

Structural formula



The CAS number is 6108-05-0

The molecular weight is 288.8

Lignocaine hydrochloride monohydrate is a white, crystalline powder that is very soluble in water, freely soluble in alcohol and practically insoluble in ether.

Lidocaine has a pKa of 7.9, an oil/water partition coefficient of 2.9, and is 65% protein-bound (mainly to alpha-1-acid glycoprotein) in plasma.

The plasma concentration of lidocaine depends upon the dose, the route of administration and the vascularity of the injection site. Peak plasma concentrations are reduced by 50% following subcutaneous injection and by 30% following epidural injection.

The concentration of lidocaine in the blood is also 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.

Lidocaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases in the order of 9.3min and 82min respectively. The slow absorption is the rate-limiting factor in the elimination of lidocaine, which explains why the apparent terminal half-life is longer after epidural administration. Absorption of lidocaine from the subarachnoid space is monophasic with an absorption half-life of 71 min.

Distribution

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 a particular affinity.

Lidocaine has a total plasma clearance of 0.95L/min, a volume of distribution at steady state of 91L, a terminal half-life of 1.6h and an estimated hepatic extraction ratio of 0.65. The clearance of lidocaine is almost entirely due to liver metabolism, and depends both on liver blood flow and the activity of metabolising enzymes.

The terminal half-life in neonates (3.2h) is approximately twice that of adults, whereas clearance is similar (10.2mL/min kg).

Lidocaine readily crosses the placenta and equilibrium with regard to the unbound concentration is rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

Lidocaine is excreted in breast milk, but in such small quantities that there is no risk of affecting the child with therapeutic doses.

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, and the main metabolites formed from lidocaine are monoethylglycine xylidide (MEGX), glycinexylidide (GX), 2,6-xylidine and 4-hydroxy-2,6-xylidine. The N-dealkylation to MEGX, is considered to be mediated by both CYP1A2 and CYP3A4. The metabolite 2,6-xylidine is converted to 4-hydroxy-2,6-xylidine by CYP2A6 and the latter is the major urinary metabolite in man. Only 3% of lidocaine is excreted unchanged. About 70% appears in the urine as 4-hydroxy-2,6-xylidine.

MEGX has a convulsant activity similar to that of lidocaine and a somewhat longer half-life. GX lacks convulsant activity and has a half-life of about 10h.

Elimination

Lidocaine has a total plasma clearance of 0.95 litres/min, a terminal half-life of 1.6h and an estimated hepatic extraction ratio of 0.65. Its rate of clearance 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).

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.

Special patient groups

The terminal half-life in neonates (3.2h) is approximately twice that of adults, whereas clearance is similar (10.2mL/min kg).

5.3 Preclinical safety data

In animal studies, the signs and symptoms of toxicity noted after high doses of lidocaine are the results of the effects of the central nervous system and cardiovascular systems. No medication related adverse effects were seen in reproduction toxicity studies, neither did lidocaine show a mutagenic potential in either *in vitro* or *in vivo* mutagenicity tests. Cancer studies have not been performed with lidocaine, due to the area and duration of therapeutic use for this medicine.

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2.6-xylidine, showed weak evidence of activity in some genotoxicity tests. The metabolite, 2,6-xylidine has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (to pH 5.0 - 7.0)
Sodium chloride
Sodium hydroxide (to pH 5.0 - 7.0) [Sodium content is 2.75mg/mL (0.119mmol/mL)]
Water for injections (to 1mL).

This preparation does not contain antioxidants or antimicrobial agents.

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

48 months from date of manufacture.

6.4 Special precautions for storage

Unopened container

Store at or below 25°C. Do not refrigerate or freeze.

Opened container

Use immediately. Discard any residue.

6.5 Nature and contents of container

10mg/mL (1%)

Lidocaine Hydrochloride Ph Eur:
20mg in 2mL ampoule (x25 dose units)
50mg in 5mL ampoule (x5 and x25 dose units) and
200mg in 20mL vial (single vial packs or pack of 5 vials).

20mg/mL (2%)

Lidocaine Hydrochloride Ph Eur:
40mg in 2mL ampoule (x25 dose units)
100mg in 5mL ampoule (x25 dose units) and
400mg in 20mL vial (single vial packs or pack of 5 vials).

*Not all pack sizes may be marketed.

Primary packaging materials

Vial stopper is composed entirely of siliconised synthetic bromobutyl rubber.

6.6 Special precautions for disposal and other handling

Compatibility

Lidocaine-Baxter injection is compatible with the following sterile diluents: 0.9% w/v sodium chloride injection; 5% w/v glucose intravenous infusion; sodium chloride intravenous infusion with glucose intravenous infusion; Lactated Ringer's (Hartmann's) solution. Solutions prepared in these diluents are stable for up to 48 hours.

Disposal

All solutions should be used immediately after opening of the container.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Lidocaine-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Lidocaine-Baxter is distributed in Australia by:
Baxter Healthcare Pty Ltd [ABN: 43 000 392 781]
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
27 September 2012.

10 DATE OF REVISION OF THE TEXT

11 March 2020.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Trade name updated to Lidocaine-Baxter. Editorial changes (including use of capitals, headings, spacing and units made consistent, removal of reference to adrenaline in tables, use of other terms other than 'drug').
4.3	Added contraindication: hypersensitivity to excipients.
4.4	Additional warnings and precautions for patients requiring special attention. Update of warnings relating to patients with acute porphyria.
4.5	Additional text relating to interactions with products affecting clearance.
4.7	Section made consistent with NZ Data Sheet Explanatory Guide and included effects relating to anaesthetic effects.
5.1	Updated data relating to pharmacodynamic actions. Pharmacokinetic information included.
5.2	Updated data relating to pharmacokinetic properties.
5.3	Preclinical data included.
6.1	List of excipients updated with relevant information.
6.5	Section updated for readability.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.