

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CITANEST[®] solution for injection
Prilocaine hydrochloride 0.5%, 2.0%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Citanest contains 5mg or 20mg of prilocaine hydrochloride per 1mL
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Citanest solution for injection is a sterile, isotonic aqueous solution. The pH of the solution is 5.0-7.0. The single dose vials and Polyamps[®] are free from preservatives and are intended for single use only.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Citanest solutions are indicated for the production of local or regional anaesthesia by the following techniques:

- local infiltration
- minor and major nerve blocks
- epidural block
- arthroscopy
- intravenous regional anaesthesia.

4.2 Dose and method of administration

Care should be taken to prevent toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. When a large dose is to be injected, e.g. in epidural block, a test dose of 3-5 mL of prilocaine containing adrenaline is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly, at a rate of 100-200 mg/min, or in incremental doses, while keeping in constant verbal contact with the patient. If toxic symptoms occur, the injection should be stopped immediately.

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 local anaesthetic used will affect the extent of spread of anaesthesia.

For a more prolonged effect, an indwelling catheter, through which the local anaesthetic may be injected, can be used. This technique is common in epidural anaesthesia and may also be used in brachial plexus anaesthesia and interpleural analgesia.

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 **Special warnings and precautions for use**). Individual variations in onset and duration occur.

Table 1 - Dosage Recommendations.

Type of block	Conc.		Dose		Indication
	mg/mL	%	mL	mg	
Lumbar epidural ^{a)}	10	1.0	30	300	Surgical operations and pain relief
	20	2.0	15-25	300-500	Surgical operations
Thoracic epidural ^{a)}	20	2.0	10-15	200-300	Surgical operations
	10	1.0	10-30	100-300	
Caudal epidural	10	1.0	20-30	200-300	Surgical operations and pain relief
	20	2.0	15-25	300-500	Surgical operations
IV Regional (Bier's block) Upper limb ^{b)} Lower limb ^{b)} i). thigh tourniquet ii). calf tourniquet	5	0.5	40	200	Surgical operations
	5	0.5	60	300	- " -
	5	0.5	40	200	- " -
Intra-articular block^{c)}	5	0.5	≤60	≤300	Arthroscopy and surgical operations
	10	1.0	≤40	≤400	- " -
Field block (eg minor nerve blocks and infiltration) Local infiltration Digital block Intercostal (per nerve) Paravertebral Retrolbulbar Peribulbar	5	0.5	≤100	≤500	Surgical operations
	10	1.0	≤ 50	≤500	- " -
	10	1.0	1-5	10-50	Surgical operations
	10	1.0	2-5	20-50	Surgical operations. Postoperative pain and fractured ribs
	10	1.0	3-5 mL	30-50 mg	Surgical operations
	20	2.0	4	80	Ocular surgery
	10	1.0	10-15	100-150	- " -
Major Nerve Block Brachial plexus: Axillary Supraclavicular, interscalene and subclavian perivascular Sciatic 3 in 1 (Femoral, obturator and lateral cutaneous)	10	1.0	40-50	400-500	Surgical operations
	10	1.0	30-40	300-400	
	20	2.0	15-20	300-400	Surgical operations
	10	1.0	30-40	300-400	Surgical operations

a) Dose includes test dose

b) Do not deflate tourniquet within 20 min of injection

c) There have been post marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. CITANEST is not approved for this indication (Also see **Special warnings and precautions for use**).

≤ = up to

NR = not recommended

PAEDIATRICS

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.

Table 2 - Dosage Recommendations in Children.

Type of block	Conc.		Dose		Indication
	mg/mL	%	mL	mg	
Caudal epidural (children above the age of 6 months)	10	1.0	0.5 mL/kg	5 mg/kg	Surgical operations

Consider both age and weight for calculation of dosages.

Prilocaine for injection is not recommended in children under 6 months of age or for use in paracervical (PCB) block and pudendal block in the obstetric patient. There is an increased risk of methaemoglobin formation in children and in the neonate after delivery.

GERIATRICS

A reduction in dosage may be necessary for elderly patients, especially those with compromised cardiovascular and/ or hepatic function.

In epidural anaesthesia a smaller dose may provide adequate anaesthesia.

WITH IMPAIRED HEPATIC FUNCTION

Although prilocaine is partly metabolised by the liver, dosage reduction is probably not warranted. However, caution should be exercised with repeated doses.

WITH IMPAIRED RENAL FUNCTION

Impairment of renal function is unlikely to affect prilocaine clearance in the short-term (24 hours). However toxicity due to accumulation may develop with prolonged or repeated administration.

4.3 Contraindications

Prilocaine solutions are contraindicated in patients with known hypersensitivity to local anaesthetics of the amide type or any of the excipients.

Prilocaine solutions are contraindicated in patients with congenital or idiopathic methaemoglobinaemia.

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medication necessary for monitoring and emergency resuscitation should 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 **Overdose**).

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention 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.
- In patients with severe anaemia or cardiac insufficiency the risk of developing methaemoglobinaemia should be considered (see **Undesirable effects**).
- Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see **Interaction with other medicines and other forms of interaction**).
- Patients with acute porphyria. Prilocaine is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients.
- Patients with severe bradycardia, cardiac conduction disturbances or severe digitalis intoxication.

Prilocaine is not recommended for use in children below the age of 6 months. Prilocaine is not recommended for use in obstetric patients under paracervical block (PCB) or pudendal block due to the risk of methaemoglobinaemia (see **Fertility, pregnancy and lactation**, and **Undesirable effects**).

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

- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.
- Retrobulbar injections may (very occasionally) reach the cranial subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.
- Retro- and peri-bulbar 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 the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors and other additives 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.
- Patients with pre-existing abnormal neurological conditions.
- 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 for CITANEST.

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

4.5 Interaction with other medicines and other forms of interaction

Prilocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmic drugs such as lignocaine, mexiletine and tocainide, since the toxic effects could be additive. Specific interaction studies with prilocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see **Special warnings and precautions for use**).

Prilocaine in high doses may cause an increase in the methaemoglobin level, particularly in conjunction with other methaemoglobin-inducing drugs e.g. sulphonamides, antimalarials and certain nitric compounds.

4.6 Fertility, pregnancy and lactation

Although prilocaine is indicated for anaesthesia in obstetrics there is no information on use of prilocaine in early pregnancy. Therefore, with the exception of its use in obstetrics, prilocaine should not be used in pregnant women, or those likely to become pregnant, unless the expected benefit outweighs any potential risk.

When used for obstetric anaesthesia in doses over 600 mg, clinically apparent maternal and foetal methaemoglobinaemia may develop, caused by prilocaine metabolites.

Neonatal methaemoglobinaemia has been reported after paracervical block (PCB) or pudendal block in the obstetric patient.

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.

It is not known to what degree prilocaine is excreted in breast milk. However, the amounts of prilocaine reaching the infant can be assumed to be very small.

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 co-ordination even in the absence of overt CNS toxicity, and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

GENERAL

The adverse reaction profile for CITANEST is similar to those of other amide local anaesthetics. Adverse reactions caused by the drug 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.

Table 3 Table of Adverse Drug Reactions (ADR)

Frequency Classification	Adverse Drug Reaction
Very Common: >1/10	<ul style="list-style-type: none"> • Vascular disorders: hypotension * • Gastrointestinal disorders: nausea *
Common >1/100 <1/10	<ul style="list-style-type: none"> • Gastrointestinal disorders: vomiting * • Nervous system disorders: paraesthesia, dizziness
Uncommon (>1/1,000 <1/100)	<ul style="list-style-type: none"> • Cardiac disorders: bradycardia • Nervous system disorders: signs and symptoms of CNS toxicity (convulsions, paraesthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, tremor, tinnitus, dysarthria, loss of consciousness) • Vascular disorders: hypertension
Rare (<1/1,000)	<ul style="list-style-type: none"> • Cardiac disorders: cardiac arrest, cardiac arrhythmias • Immune system disorders: allergic reactions, anaphylactic reaction • Respiratory disorders: respiratory depression • Nervous system disorders: neuropathy, peripheral nerve injury, arachnoiditis • Blood and lymphatic system disorders: methaemoglobinaemia (See OVERDOSE) and cyanosis. • Eye disorders: diplopia

*ADRs occur more frequently after epidural blocks.

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 occur due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see **Special warnings and precautions for use**). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, lightheadedness, 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 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 drug from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug 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, injections of the local anaesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be 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.

METHAEMOGLOBINAEMIA

Methaemoglobinaemia may occur after the administration of prilocaine. The repeated administration of prilocaine, even in relatively small doses, can lead to clinically overt methaemoglobinaemia (cyanosis). Prilocaine is therefore not recommended for continuous techniques of regional anaesthesia.

The conversion of haemoglobin to methaemoglobin is caused by the prilocaine metabolite, orthotoluidine, which has a long half-life and tends to accumulate, and in turn, is converted to 4- and 6-hydroxytoluidine. Methaemoglobin has risen to clinically significant levels in patients receiving high doses of prilocaine. Cyanosis occurs when the methaemoglobin concentration in the blood reaches 1-2 g/100 mL (6-12% of the normal haemoglobin concentration). Methaemoglobin oxidises only slowly back to haemoglobin, although this process can be greatly accelerated by the intravenous injection of methylene blue (see below).

The reduction in oxygen-carrying capacity due to the administration of prilocaine in normal patients is marginal; hence, the methaemoglobinaemia is usually symptomless. However, in severely anaemic patients it may cause hypoxaemia. It is important to rule out other more serious causes of cyanosis such as acute hypoxaemia and/or heart failure.

In neonates and small infants there is an increased risk of development of methaemoglobinaemia (see **Dose and method of administration**, and **Special warnings and precautions for use**).

Note: Even low concentrations of methaemoglobin may interfere with pulse oximetry readings, indicating a false low oxygen saturation.

TREATMENT OF METHAEMOGLOBINAEMIA

If clinical methaemoglobinaemia occurs, it can be rapidly treated by a single intravenous injection of a 1% methylene blue solution, 1 mg/kg body weight, over a 5-minute period. Cyanosis will disappear in about 15 minutes. This dose should not be repeated as methylene blue in high concentrations acts as a haemoglobin oxidant.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.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 (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration (see **Undesirable effects**).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Prilocaine hydrochloride is a local anaesthetic of the amide type. It is similar to lignocaine in having a rapid onset and a medium duration of action. The 2% solution will last 1½-2 h when given epidurally, and up to 4 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. The peak plasma concentrations of prilocaine are lower than those associated with the same dose of lignocaine and it is also more quickly eliminated. Prilocaine has a lower acute toxicity than lignocaine.

Onset and duration of the local anaesthetic effect of prilocaine depend on the dose and the site of administration. However, its propensity for causing methaemoglobinaemia makes it unsatisfactory for continuous techniques.

Prilocaine, 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 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 local anaesthetic reach the systemic

circulation, symptoms and signs of toxicity may appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity occurs at lower plasma concentrations (see **Undesirable effects**) and usually precedes the cardiovascular effects. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventual 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

Prilocaine has a pKa of 7.89 and an N-heptane/pH 7.4 buffer partition coefficient of 0.9. Prilocaine has an octanol:water partition ratio of 25 at pH 7.4, and is 40% protein bound (mainly to alpha-1-acid glycoprotein) in plasma.

The peak plasma concentration after prilocaine administration depends on the dose, the route of administration, vascularity of the injection site and the concomitant administration of vasoconstrictor agents. A linear relationship exists between the amount of prilocaine administered and the resultant peak plasma concentration in the dose range 200-600 mg.

The highest plasma concentrations will occur after intercostal nerve block, followed in order of decreasing concentration by injection into the lumbar epidural space, major nerve blocks such as brachial plexus and subcutaneous tissue.

The higher concentrations following intercostal administration may be related to the multiple injections required for this technique, whereby the solution is exposed to a greater vascular area, which results in a greater rate of absorption. On the other hand, the large amount of adipose tissue in the lumbar epidural space will tend to retard vascular absorption.

Prilocaine has a mean total plasma clearance of 2.37 L/min, a large apparent distribution volume of between 190 L and 260 L, and the terminal half-life of prilocaine is 1.6 h.

Only a small proportion of prilocaine (less than 5%) is excreted unchanged in the urine. *In vitro* and animal studies have shown metabolism of prilocaine by lung and kidney tissues.

In the liver, prilocaine is primarily metabolized by amide hydrolysis to ortho-toluidine and N-propylamine. Ortho-toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2-amino-5-hydroxytoluene, metabolites which are believed to be responsible for the occurrence of methaemoglobinaemia.

It is uncertain to what extent disease states like severe liver cirrhosis and congestive heart failure influence the disposition of prilocaine.

Prilocaine readily passes the placenta and free plasma concentrations are similar in both foetus and mother. In the presence of foetal acidosis, they may be slightly higher in the foetus, due to ion trapping. Information concerning the elimination half-life of prilocaine in neonates is not available.

5.3 Preclinical safety data

In animal studies, the symptoms and signs of toxicity noted after high doses of prilocaine are the results of the effects on the central nervous and cardiovascular systems. A mild methaemoglobinaemia was seen in a single study in rats, after repeated dosing. This is also occasionally seen in the therapeutic situation as a result of prilocaine overdose or off-label use. No drug related adverse effects were seen in reproduction toxicity studies, neither did prilocaine show mutagenic potential in either in vitro or in vivo mutagenicity tests. Cancer studies have not been performed with prilocaine, due to the area and duration of therapeutic use for this drug.

Prilocaine did not show any mutagenic potential in either in vitro or in vivo mutagenicity tests. Cancer studies have not been performed with prilocaine due to the indication and duration of therapeutic use of this medicine.

A metabolite of prilocaine, ortho-toluidine, showed evidence of mutagenic activity. The metabolite ortho-toluidine 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 prilocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium chloride
- Sodium hydroxide (for pH adjustment)
- Water for injection

6.2 Incompatibilities

The solubility of prilocaine is limited at pH >7.0. This must be taken into consideration when alkaline solutions, i.e. carbonates are added since precipitation might occur.

6.3 Shelf life

Single Dose Vials	36 months
Plastic ampoules (Polyamp®)	24 months

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

CITANEST 0.5% 5 x 50 mL Single Dose Vials
CITANEST 2.0% 10 x 5 mL Polyamp® Duofit®

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited

Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Telephone: (09) 918 5100
Email: aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

10 November 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Management of hypotension and bradycardia related to epidural anaesthesia is updated.

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