NAME OF THE MEDICINE

The active ingredient in CITANEST is prilocaine hydrochloride. The CAS number for prilocaine hydrochloride is 1786-81-8. The Australian Approved Name is prilocaine hydrochloride.

The chemical structure of prilocaine hydrochloride is

\[
\begin{align*}
\text{CH}_3 & \\
- & \\
\text{NHCOCHCH}_3 & \\
\text{NHCH}_2\text{CH}_2\text{CH}_3 & \text{HCl}
\end{align*}
\]

DESCRIPTION

The chemical name for prilocaine hydrochloride is 2-propylamino propiono-o-toluidide hydrochloride; also known as propitocaine hydrochloride.

Prilocaine hydrochloride has a pKₐ of 7.89. Prilocaine base, which has a molecular weight of 220.3, is only slightly soluble in water. Prilocaine hydrochloride is soluble 1:5 in water.

CITANEST solution for injection is a sterile, isotonic aqueous solution with a pH of 5.0 - 7.0. CITANEST solution for injection contains the following inactive ingredients: sodium chloride, water for injection, hydrochloric acid and/or sodium hydroxide for pH adjustment.

Prilocaine is classed as a membrane stabilising agent and is a local anaesthetic of the amide type.

PHARMACOLOGY

Prilocaine stabilises the neuronal membrane and reversibly prevents the initiation and conduction of nerve impulses thereby producing local anaesthesia. Prilocaine hydrochloride has a similar time of onset and potency to lignocaine. Prilocaine has lower CNS toxicity than lignocaine. The onset and duration of anaesthesia depend on the route of administration, status of the patient and the dosage (volume and concentration) employed.
Prilocaine is absorbed more slowly than lignocaine due to its lower vasodilator effect and has different distribution, degradation and excretion patterns. Amidases in the liver, kidneys and lungs metabolise prilocaine directly. One metabolite excreted in the urine is O-toluidine which is believed to cause the methaemoglobinaemia observed after large doses of prilocaine (see PRECAUTIONS and ADVERSE REACTIONS).

INDICATIONS

CITANEST solutions are indicated for the production of local or regional anaesthesia by infiltration techniques; intravenous regional anaesthesia; by peripheral nerve block techniques such as intercostal blocks; major plexus blocks such as brachial plexus blocks and by epidural and subarachnoid blocks.

CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics or other components of the injection solution. Detection of suspected sensitivity by skin testing is of limited value.

2. Congenital or idiopathic methaemoglobinaemia.

3. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension.

4. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and in the presence of septicaemia.

5. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with coagulation disorders or receiving anti-coagulation treatment.

See also DRUG INTERACTIONS

PRECAUTIONS

1. WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS.

BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED. DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDER-VENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND DEATH.
2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS.

3. ALTHOUGH INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS FOLLOWING ARTHROSCOPIC AND OTHER SURGICAL PROCEDURES IS AN UNAPPROVED USE, THERE HAVE BEEN POST-MARKETING REPORTS OF CHONDROLYSIS IN PATIENTS RECEIVING SUCH INFUSIONS. THE MAJORITY OF REPORTED CASES OF CHONDROLYSIS HAVE INVOLVED THE SHOULDER JOINT; CASES OF GLENO-HUMERAL CHONDROLYSIS HAVE BEEN DESCRIBED IN PAEDIATRIC AND ADULT PATIENTS FOLLOWING INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS WITH AND WITHOUT ADRENALINE FOR PERIODS OF 48 TO 72 HOURS. THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHETHER SHORTER INFUSION PERIODS ARE NOT ASSOCIATED WITH THESE FINDINGS. THE TIME OF ONSET OF SYMPTOMS, SUCH AS JOINT PAIN, STIFFNESS AND LOSS OF MOTION CAN BE VARIABLE, BUT MAY BEGIN AS EARLY AS THE 2ND MONTH AFTER SURGERY. CURRENTLY, THERE IS NO EFFECTIVE TREATMENT FOR CHONDROLYSIS; PATIENTS WHO EXPERIENCED CHONDROLYSIS HAVE REQUIRED ADDITIONAL DIAGNOSTIC AND THERAPEUTIC PROCEDURES AND SOME REQUIRED ARTHROPLASTY OR SHOULDER REPLACEMENT. THEREFORE, CITANEST SHOULD NOT BE USED FOR POST-OPERATIVE INTRA-ARTICULAR CONTINUOUS INFUSION.

4. The safety and effectiveness of CITANEST depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

5. The lowest dosage that results in effective anaesthesia should be used (see DOSAGE AND ADMINISTRATION). Repeated injection of CITANEST may cause accumulation of prilocaine or its metabolites and result in toxic effects.

Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their age and physical status.

6. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological conditions.

7. The possibility of hypotension and bradycardia following epidural or subarachnoid blockade should be anticipated and precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor drugs and oxygen.

8. Prilocaine should be given with great caution to patients with severe bradycardia, cardiac conduction disturbances or severe digitalis intoxication. 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.

9. Local anaesthetics should be used in caution in patients with partial or complete heart block due to the fact that local anaesthetics may depress myocardial conduction.

10. Since prilocaine is partly metabolised in the liver and excreted via the kidneys, the possibility of drug accumulation should be considered in patients with hepatic and/or renal impairment (see DOSAGE AND ADMINISTRATION).

11. In patients with hypoxemia e.g. as a result of severe anaemia, cardiac insufficiency etc, large doses of prilocaine may produce methaemoglobinaemia, increasing the potential for further hypoxic embarrassment (see ADVERSE REACTIONS).

12. Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses.

Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following the use of local anaesthetic injections for retrobulbar block. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures.

Retrobulbar injections may very occasionally reach the cranial subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions.

Retro- and peri-bulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes of this 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.

13. Paracervical block or pudendal block with prilocaine is not recommended in the obstetric patient (see USE IN PREGNANCY). There is an increased risk for methaemoglobin formation in the neonate after delivery.

14. Paracervical block can sometimes cause fetal bradycardia/tachycardia, and careful monitoring of the fetal heart rate is necessary (see USE IN PREGNANCY).

15. Prilocaine should be used with caution in patients with known drug sensitivities. Patients allergic to ester derivatives of para-aminobenzoic acid (procaine, tetracaine, benzocaine etc.) have not shown cross sensitivity to agents of the amide type.
16. 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.

17. Prilocaine should be used with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully established.

18. Use in children below the age of 6 months is not recommended due to risk of methaemoglobinaemia.

19. 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.

Use in pregnancy  Category A

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

Prilocaine crosses the placenta and almost equal concentrations have been found in fetal and maternal blood following epidural blocks. During prolonged epidural blockade, prilocaine may cause maternal and fetal methaemoglobinaemia which could lead to fetal hypoxia.

However, if prilocaine is used for paracervical block, fetal heart rate should always be monitored since fetal bradycardia/tachycardia frequently follows paracervical block and may be associated with foetal acidosis and hypoxia. The possible undesired consequences of a paracervical block should be weighed against its advantages when fetal distress is expected or when factors predisposing to fetal distress are present (such as toxaemia, prematurity, diabetes).

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

Use in lactation

It is not known whether prilocaine or its metabolites appear in breast milk.

Effects on ability to drive and operate machinery

Depending on dosage local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and coordination.
Genotoxicity

There was no evidence for genotoxicity of prilocaine in assays for gene mutation (bacterial reverse mutation) or chromosomal damage (human lymphocytes in vitro, mouse micronucleus test). A metabolite of prilocaine, o-toluidine, has shown evidence for induction of DNA adducts and clastogenicity.

Carcinogenicity

Carcinogenicity assays have not been conducted with prilocaine. A metabolite of prilocaine, o-toluidine, is carcinogenic in rodent bioassays and, based on analysis of cancer incidence in occupationally-exposed human populations, has been categorised as carcinogenic to humans. Risk assessments comparing expected human exposure to o-toluidine from infrequent/short term use of prilocaine with carcinogenic doses in rodent studies suggest a wide margin of safety for clinical use. This margin may be reduced with frequent/long term treatment with prilocaine.

Significant drug interactions

1. Anti-arrhythmic drugs
   Local anaesthetics of the amide type such as 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 and mexiletine since the toxic effects may be additive. Specific interaction studies with prilocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised.

2. Methaemoglobin
   Drugs which may predispose to methaemoglobin formation, e.g. sulfonamides, antimalarials and certain nitric compounds, could potentiate this adverse effect of prilocaine.

3. 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.

ADVERSE EFFECTS

Reactions to prilocaine are similar in character to those observed with other local anaesthetics of the amide type.

Adverse reactions may be due to high plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection. Pronounced acidosis or hypoxia may increase the risk and severity of toxic reactions.

Such reactions are systemic in nature and involve the central nervous system and/or cardiovascular system (see OVERdosage). Inadvertent subarachnoid injection may lead to cardiovascular collapse, CNS depression and respiratory arrest.
More common reactions
Nervousness, dizziness, blurred vision, tremor, drowsiness, tinnitus, numbness, disorientation, hypotension, nausea and vomiting.

Less common reactions
More serious but less common reactions that reflect an overdosage of prilocaine are paraesthesia circumoral, numbness of the tongue, hyperacusis, dysarthria, convulsions, unconsciousness, respiratory depression or arrest, cardiovascular collapse and bradycardia which may lead to cardiac arrest.

Hypertension, cardiac arrhythmias and diplopia have also been observed.

Regarding methaemoglobinaemia, see below.

Allergy:
Allergy to amide type local anaesthetics is rare but may present as allergic dermatitis, bronchospasm or anaphylaxis.

Methaemoglobinaemia:
Methaemoglobinaemia and cyanosis may occur following the administration of prilocaine solutions, particularly following a high dose. This is caused by the metabolite O-toluidine. Cyanosis of the nails and lips are clinical signs of methaemoglobinaemia. A dose-response relationship appears to exist between the amount of prilocaine administered and the degree of methaemoglobin formation. In studies conducted in man, the incidence of methaemoglobinaemia at a dose of 400 mg prilocaine was not statistically significant. Cases of cyanosis at doses between 400 mg and 600 mg prilocaine are extremely rare.

At a dose of 600 mg prilocaine, methaemoglobin forms at levels less than 15% of the total haemoglobin content. This degree of methaemoglobinaemia is not associated with any adverse respiratory, cardiovascular or CNS symptoms. However, cyanosis has been reported at this dosage level.

If methaemoglobinaemia does occur, it may be treated by a single intravenous injection of a 1% methylene blue solution, given at a dose of 1 mg/kg body weight over a 5 minute period. This dose normally reverses methaemoglobinaemia within 15 minutes and should not be repeated as methylene blue in high concentrations acts as a haemoglobin oxidant.

In most patients receiving doses of CITANEST within the recommended range the appearance of clinical signs and symptoms of hypoxia may be due to cardiac or respiratory insufficiency and should be treated with oxygen and/or other appropriate measures. If cyanosis persists, methaemoglobinaemia should be suspected and methylene blue treatment initiated.

In neonates and small infants there is an increased risk of development of methaemoglobinaemia. Hence prilocaine should not be used for paracervical block or pudendal block in the obstetric patient and in children under the age of 6 months.
Note: Even low concentrations of methaemoglobin may interfere with pulse oximetry readings, indicating a false low oxygen saturation.

Neurological reactions:
The incidence of adverse neurological reactions directly caused by the use of local anaesthetics is very low.

Neurological reactions may be related to the total dose of the local anaesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these effects may be related to local anaesthetic techniques, with or without contribution from the drug. Neurological reactions after regional anaesthesia have included persistent anaesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control, anterior spinal artery occlusion, neuropathy, nerve trauma and arachnoiditis.
DOSAGE AND ADMINISTRATION

The lowest dosage that results in effective anaesthesia should be used and should be based on the status of the patient and the type of regional anaesthesia intended.

Adults

RECOMMENDED DOSAGES FOR CITANEST PLAIN SOLUTIONS FOR VARIOUS ANAESTHETIC PROCEDURES IN THE AVERAGE, HEALTHY, 70 KG ADULT PATIENT.

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>CONCENTRATION</th>
<th>VOLUME mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Plain</td>
</tr>
<tr>
<td>INFILTRATION</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>INTRAVENOUS REGIONAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Extremities</td>
<td>0.5</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Lower Extremities</td>
<td>0.5</td>
<td>60 - 80</td>
</tr>
<tr>
<td>PLEXUS NERVE BLOCKS</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>Brachial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERIPHERAL NERVE BLOCKS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercostal</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>1.0</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Sciatic femoral</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>EPIDURAL*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1.0</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Analgesia</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Anaesthesia</td>
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<td>20</td>
</tr>
<tr>
<td>Caudal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesia</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>2.0</td>
<td>20</td>
</tr>
</tbody>
</table>

* Dose determined by number of segments to be anaesthetised (2-3 mL/segment)

Note:

1. Recommended doses

   Toxic doses vary widely between patients and toxic effects may occur after any local anaesthetic procedure. Careful observation of the patient must therefore be maintained. It is recommended that the dose of prilocaine at any one time should not exceed 6 mg/kg (plain solutions).
However, the dose administered must be tailored to the individual patient and procedure, and the maximum doses here quoted should be used as a guide only.

2. **Hypotension:**
   During thoracic, lumbar and caudal epidural anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses, improper positioning of the patient or accidental disposition of the anaesthetic within the subarachnoid space. Hypotension and bradycardia may occur as a result of sympathetic blockade.

3. **Test dose**
   For epidural anaesthesia, a 3 - 5mL test dose of a local anaesthetic solution preferably containing 15 micrograms of adrenaline should be administered. Verbal contact and repeated monitoring of the heart rate and blood pressure should be maintained for 5 minutes after the test dose after which, in the absence of signs of subarachnoid or intravascular injection, the main dose may be given.

   Use of a test dose containing adrenaline may have further advantages in that an intravascular injection of adrenaline will be quickly recognised by an increase in heart rate, usually within about 40 seconds. To detect this, the heart rate and rhythm should be monitored with an electrocardiogram.

   Prior to administration of the total dose, aspiration should be repeated. The main dose should be injected slowly, with continual assessment of the patient. If toxic symptoms or signs occur, the injection should be stopped immediately.

**Paediatrics**
Experience with prilocaine in children under the age of 10 is limited. A reduced dosage based on body weight or surface area should be used. The dosage should be calculated for each patient individually and modified in accordance with the physician's experience and knowledge of the patient and with reference to standard textbooks of paediatric anaesthesia. Prilocaine for injection is not recommended in children under 6 months of age or for use in paracervical block and pudendal block in the obstetric patient. There is an increased risk for methaemoglobin formation in children under 6 months of age and 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.
OVERDOSAGE

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see ADVERSE REACTIONS and PRECAUTIONS).

Systemic toxicity to amide type local anaesthetics is initially manifested as CNS excitation and may result in the slow onset of nervousness, dizziness, blurred vision and tremors followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

Toxic cardiovascular reactions to local anaesthetics are usually depressant in nature, may occur rapidly and with little warning and can lead to peripheral vasodilation, hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of overdosage

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

If convulsions occur then immediate attention is required for the maintenance of a patent airway and assisted or controlled ventilation with oxygen, via a positive airway pressure delivery system mask. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously.

Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, appropriate anticonvulsant medication such as an ultra-short acting barbiturate (e.g. thiopentone) or a benzodiazepine (e.g. diazepam) may be administered IV. The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics.

If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary.

PRESENTATION AND STORAGE CONDITIONS

Citanest® 0.5% plain
(prilocaine hydrochloride 5 mg/mL)
50 mL single dose vial.

Citanest® 1.0% plain
(prilocaine hydrochloride 10 mg/mL)
5 mL polyethylene ampoule (Polyamp DuoFit®) Not Marketed in Australia.

Citanest® 2.0% plain
(prilocaine hydrochloride 20 mg/mL)
2 mL ampoule, 5 mL polyethylene ampoule (Polyamp DuoFit®) Not marketed in Australia.

Prilocaine solutions should be stored below 25°C.
Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between CITANEST solutions and metal surfaces such as metal bowls, cannulae and syringes with metal parts.

The product contains no antimicrobial preservative. An ampoule or single dose vial should be used on one patient on one occasion only. Solutions showing discolouration and unused portions of solutions from single dose vials and ampoules should be discarded.

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road, North Ryde
NSW 2113 Australia

Date of TGA approval: 1 March 2011

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