

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prilocaine hydrochloride 1% Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of sterile, clear, aqueous solution contains prilocaine hydrochloride 10 mg.

Excipient(s) with known effect:

Each millilitre (ml) of Prilocaine hydrochloride 1% Solution for Injection contains 2.36 mg of sodium, equivalent to 118 mg per 50 ml ampoule.

Prilocaine hydrochloride 1% Solution for Injection contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prilocaine hydrochloride is indicated in adults and children aged above 6 months as a local anaesthetic for use in infiltration anaesthesia and nerve blocks.

4.2 Posology 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.

Posology

The dose is adjusted according to the response of the patient and the site of administration.

The lowest concentration and smallest dose producing the required effect should be given.

The maximum dose of prilocaine hydrochloride for healthy adults should not exceed 400 mg.

Older People

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

Paediatric population

Prilocaine hydrochloride should not be used in children under 6 months of age and 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.

In children above the age of 6 months the dosage can be calculated on a weight basis up to 5 mg/kg.

There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Prilocaine hydrochloride is not approved for this indication (see also Section 4.4).

Preservative containing solutions i.e. those supplied in multi-dose vials should not be used for intrathecal or epidural anaesthesia, intraocular or retrobulbar injections or in doses of more than 15 ml for other types of blockades.

4.3 Contraindications

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

Hypersensitivity to methyl and/or propyl parahydroxybenzoate (methyl-/propyl paraben), or to their metabolite para-aminobenzoic acid (PABA).

Formulations of prilocaine containing parabens should be avoided in patients allergic to ester local anaesthetics or its metabolite PABA.

Prilocaine hydrochloride should be avoided in patients with anaemia or congenital or acquired methaemoglobinaemia.

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area, with the equipment and drugs necessary for monitoring an emergency resuscitation immediately available. When performing major blocks, an i.v. 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 section 4.9).

Great caution must be exercised to avoid accidental intravascular injection of this compound, since it may give rise to the rapid onset of toxicity, with marked restlessness, twitching, or convulsions, followed by coma with apnoea and cardiovascular collapse.

Special Patient Groups

In common with other local anaesthetics, prilocaine hydrochloride should be used cautiously in the elderly, patients in poor health, patients with epilepsy, severe or untreated hypertension, impaired cardiac conduction, severe heart disease, impaired respiratory function, and in patients with liver or kidney damage, if the dose or site of administration is likely to result in high blood levels.

Patients with cardiac insufficiency require special attention due to the risk of developing methaemoglobinaemia (see section 4.8).

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 section 4.5).

Prilocaine hydrochloride solution for injection 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 case of vulnerable patients.

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

- 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 the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used.
- Injections in the head and neck regions may be made inadvertently into an artery, causing cerebral symptoms even at low doses.

Methaemoglobinaemia may occur at lower doses of prilocaine in patients suffering from anaemia, from congenital or acquired haemoglobinopathy (including methaemoglobinaemia), or in patients receiving concomitant therapy e.g. sulphonamides, known to cause such conditions. Infants are

particularly susceptible, due to a lower activity of the enzyme which reduces methaemoglobin to haemoglobin. Hence prilocaine is not recommended for paracervical block (PCB) or pudendal block in the obstetric patient and in children under the age of 6 months (see sections 4.6 and 4.8).

Local anaesthetics should be avoided when there is inflammation at the site of the proposed injection.

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 prilocaine hydrochloride.

Preservative containing solutions i.e. those supplied in multi-dose vials should not be used for intrathecal or epidural anaesthesia, intraocular or retrobulbar injections or in doses of more than 15 ml for other types of blockades.

4.5 Interaction with other medicinal products and other forms of interaction

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

Prilocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type anaesthetics, since the toxic effects are additive.

Specific interaction studies with prilocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of prilocaine hydrochloride during early pregnancy.

Neonatal methaemoglobinaemia has been reported after paracervical block (PCB) or pudendal block in the obstetric patient (see section 4.4).

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

Prilocaine enters the mothers milk but no effects of prilocaine have been shown in breastfed newborns/infants of treated mothers.

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

The adverse reaction profile for prilocaine hydrochloride 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.

The adverse reactions considered at least possibly related to treatment with prilocaine hydrochloride from clinical trials with related products and post-marketing experience are listed below by body system organ class and absolute frequency. Frequencies are defined as ‘very common’ ($\geq 1/10$), ‘common’ ($\geq 1/100$ to $< 1/10$), ‘uncommon’ ($\geq 1/1,000$ to $< 1/100$), ‘rare’ ($\geq 1/10,000$ to $< 1/1,000$), or ‘not known’ (cannot be estimated from the available data).

Table of Adverse Drug Reactions (ADRs)

System Organ Class	Frequency Classification	Adverse Drug Reaction
Blood and lymphatic system disorders	Rare	Methaemoglobinaemia (see below), cyanosis*
Immune system disorders	Rare	Allergic reactions (including urticaria, oedema, dyspnoea), anaphylactic reactions
Nervous system disorders	Common	Paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (see below)
	Rare	Neuropathy, peripheral nerve injury
Eye disorders	Not known	Diplopia

System Organ Class	Frequency Classification	Adverse Drug Reaction
Cardiac disorders	Common	Bradycardia
	Rare	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Very common	Hypotension**
	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression
Gastrointestinal disorders	Very common	Nausea**
	Common	Vomiting**

* In the presence of methaemoglobinaemia.

** 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 appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4). 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, 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 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 drugs.

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.

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). 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 sections 4.2 and 4.4).

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 section 4.8 Acute systemic toxicity and Treatment of acute systemic toxicity).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, ATC code: NO1B B04

Prilocaine is a local anaesthetic of the amide type. Local anaesthetics act by preventing transmission of impulses along nerve fibres and at nerve endings; depolarisation and ion-exchange are inhibited. The effects are reversible.

Prilocaine has a fast onset and a medium duration of action. The 2% solution will last 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.

Onset and the 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.

5.2 Pharmacokinetic properties

Prilocaine hydrochloride is absorbed more slowly than lidocaine (lignocaine) because of its slight vasoconstrictor action but its half-life in blood is less than that of lidocaine (lidocaine half-life approximately 10 minutes, elimination half-life approximately 2 hours).

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.

Amidases in the liver and kidney metabolise prilocaine directly.

In the liver, prilocaine is primarily metabolised by amide hydrolysis to orthotoluidine and N-propylamine. O-Toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2-amino-5-hydroxytoluene, metabolites with long half-lives that tend to accumulate and are believed to be responsible for the occurrence of methaemoglobinaemia.

5.3 Preclinical safety data

Prilocaine hydrochloride is a well established active ingredient.

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 indication and duration of therapeutic use of this drug.

The main metabolite of prilocaine, o-toluidine, has been shown to be genotoxic and is also carcinogenic in preclinical toxicological studies evaluating chronic exposure. The clinical relevance of the observed carcinogenicity of o-toluidine following chronic exposure compared to the intermittent use of prilocaine for local anaesthesia is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide/hydrochloric acid for pH adjustment, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Multi-dose glass vials of 20ml and 50ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive,
Citywest Business Campus,
Dublin 24, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/0073

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
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14/05/2002

10 DATE OF REVISION OF THE TEXT

05/07/2022