

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prilotekal 20mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 20 mg of prilocaine hydrochloride (equivalent to 2%)

1 ampoule with 5 ml solution, contains 100 mg of prilocaine hydrochloride

Excipients:

0.0086 mg sodium per 1 ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Clear, colourless solution.

The pH is between 5.0 and 6.0. The solution is hyperbaric with osmolality comprised between 490 and 540 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prilotekal is indicated in adults for spinal anaesthesia in short term surgical procedures (see section 4.2).

4.2 Posology and method of administration

Restricted to hospital use only

Spinal anaesthesia must only be administered by (or under the supervision of) specialist medical personnel with the necessary knowledge and experience (see section 4.4).

The equipment, drugs and personnel capable of dealing with an emergency, e.g. maintaining the patency of the airways and administering oxygen, must be immediately available, since in rare cases severe reactions, sometimes with a fatal outcome, have been reported after using local anaesthetics, even in the absence of individual hypersensitivity in the patient's case history.

If signs of acute systemic toxicity or total spinal block are observed, the injection of the local anaesthetic must be stopped immediately (see section 4.4).

Posology

Posology must be established on an individual basis in accordance with the characteristics of the specific case. When determining the dose, take into consideration the patient's physical condition and the concomitant administration of other medicinal products. The lowest possible dose should be chosen.

The duration of action is dose-dependent.

The indications relating to recommended doses are valid in adults of average height and weight (approximately 70 kg) for obtaining an effective block with one single administration. There are wide individual variations with regard to extent and duration of action. The experience of the anaesthetist and knowledge of the patient's general condition are essential for establishing the dose.

With regard to posology the following guidelines are applied:

Adults population

<i>Extension of sensory blockade required T10</i>	ml	mg	<i>Average duration of action (minutes)</i>
	2-3	40-60	Approx. 100-130

As a general guideline, the maximum recommended dose is 80 mg of prilocaine hydrochloride (= 4 ml Prilotekal).

Paediatric population

The safety and efficacy of Prilotekal in paediatric population have not been established. No data are available.

The use of Prilotekal in children and adolescents is not recommended

The use of Prilotekal in children younger than 6 months is contraindicated (see section 4.3)

Special population

It is advisable to reduce the dose in patients in a compromised general condition. In addition, in patients with established concomitant disorders (e.g. vascular occlusion, arteriosclerosis, diabetic polyneuropathy) a reduced dose is indicated.

In the case of compromised liver or kidney function a lower dosage range is recommended.

Method of administration

Due to the glucose content Takipril is only to be used for spinal anaesthesia. It is not recommended for the use in epidural anaesthesia

Inject Prilotekal via intrathecal route into the intervertebral space L2/L3, L3/L4 and L4/L5.

Administer the injection slowly, after having aspirated a minimum quantity of CSF to confirm the correct position and check the patient's vital functions extremely carefully maintaining continuous verbal contact.

If signs of acute systemic toxicity or total spinal block are observed, the injection of the local anaesthetic must be stopped immediately (see section 4.4).

If the patient is in a seated position, the injected solution diffuses mainly in a caudal direction (in the direction of the sacrum); if the patient is lying down, the anaesthetic diffuses by gravity according to the patient's position (Trendelenburg and anti-Trendelenburg).

By means of the excipient glucose, the density of Prilotekal is 1.026 g/g at 20°C, equivalent to 1.021 g/g at 37°C.

4.3 Contraindications

Prilotekal must not be used in patients with

- hypersensitivity to prilocaine hydrochloride, other amide-type local anaesthetics or to any of the excipients listed in section 6.1,

- serious problems with cardiac conduction,
- severe anaemia,
- decompensated cardiac insufficiency,
- cardiogenic and hypovolemic shock,
- congenital or acquired methemoglobinemia.
- concomitant anticoagulant therapy general and specific contraindications for the technique of subarachnoid anaesthesia.

The use of Prilotekal in children younger than 6 months is contraindicated due to a higher risk of developing methemoglobinemia

The intravascular injection of Prilotekal is contra-indicated. Prilotekal must not be injected into infected areas.

4.4 Special warnings and precautions for use

Due to the glucose content Prilotekal is only to be used for spinal anaesthesia. It is not recommended for the use in epidural anaesthesia.

Prilocaine may potentiate the formation of methemoglobin by medicinal products known to induce methemoglobin (see section 4.5).

Spinal anaesthesia must only be administered by (or under the supervision of) specialist medical personnel with the necessary knowledge and experience. The doctor in charge is responsible for taking the measures needed to avoid an intravascular injection.

In addition, it is essential for the doctor to know how to recognize and treat undesirable effects, systemic toxicity and other complications. If signs of acute systemic toxicity or total spinal block are observed, the injection of the local anaesthetic must be stopped immediately (see section 4.9).

Some patients require special attention in order to reduce the risk of serious undesirable effects, even when locoregional anaesthesia constitutes the optimum choice for the surgical intervention:

- Patients with total or partial heart block, since local anaesthetics can suppress myocardial conduction.
- Patients with high grade cardiac decompensation. The risk of methemoglobinemia must also be taken into consideration (see section 4.8).
- Patients with advanced liver or kidney damage.
- Elderly patients and patients in reduced general condition.
- Patients treated with class III antiarrhythmic agents (e.g. amiodarone). These patients should be subjected to careful observation and ECG monitoring, since cardiac effects may be added (see section 4.5).

- In patients with acute porphyria, Prilotekal should only be administered when there is a compelling indication for its use, as Prilotekal may potentially precipitate porphyria. Appropriate precaution should be taken in all patients with porphyria.

Ensuring the presence of reliable venous access is recommended.

As with all local anaesthetics, a drop in arterial pressure may occur and cardiac frequency may slow.

In high risk patients, the recommendation is to improve their general condition prior to the intervention.

A rare, but serious, undesirable effect of spinal anaesthesia is high or total spinal block, with consequent cardiovascular and respiratory depression. Cardiovascular depression is induced by an extended block of the sympathetic nervous system, which may induce severe hypotension and bradycardia to the point of cardiac arrest. Respiratory depression is induced by the block of the respiratory musculature and the diaphragm.

Especially in elderly patients and patients in the final period of pregnancy there is an increased risk of high or total spinal block: consequently it is advisable to reduce the anaesthetic dose.

Particularly in the case of elderly patients, an unexpected drop in arterial pressure may occur as a complication of spinal anaesthesia.

Rarely, neurological damage may occur after spinal anaesthesia, manifesting as paresthesia, loss of sensitivity, motor weakness and paralysis. Occasionally these symptoms persist.

There is no evidence that neurological disorder, such as multiple sclerosis, hemiplegia, paraplegia or neuromuscular disorders may be negatively influenced by spinal anaesthesia. Nevertheless, it should be used with care. Careful evaluation of the risk-benefit ratio is recommended prior to treatment.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (maximum dose equal to 4 ml of Prilotekal), i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Prilocaine may potentiate the formation of methemoglobin by medicinal products known to induce methemoglobin (e.g. sulfonamides, antimalarials, sodium nitroprussiate and nitroglycerin).

In the event of the concomitant use of prilocaine and other local anaesthetics or medicinal products with a chemical structure similar to prilocaine, e.g. certain antiarrhythmics such as aprindine, lidocaine, mexiletine and tocainide, it is possible for undesirable effects to be added. No studies have been performed on interactions between prilocaine and class III antiarrhythmics (e.g. amiodarone), but care must also be taken in this case (also see section 4.4).

The combination of various local anaesthetics induces additional effects which affect the cardiovascular system and the CNS.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of prilocaine in pregnant women. Prilocaine is able to cross the placenta. Cases of neonatal methaemoglobinaemia requiring treatment have been reported following paracervical block or pudendal anaesthesia with prilocaine during obstetric use. Cases of foetal bradycardia with fatalities have occurred with other local amide-type anaesthetics following paracervical block. Studies in animals have shown developmental toxicity (see section 5.3).

Prilotekal may therefore only be administered in cases where there is a compelling indication for its use. Use of prilocaine for paracervical block or pudendal anaesthesia should be avoided.

Breast-feeding

It is not known whether prilocaine passes into breast milk. If administration is required during lactation, breast-feeding can be resumed approximately 24 hours after treatment.

Fertility

No human data on the effect of prilocaine on fertility are available. Prilocaine had no effect on the fertility of male and female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

In the case of using Prilocaine hydrochloride hyperbar, the doctor is responsible for deciding in each individual case if the patient can drive or use machines.

4.8 Undesirable effects

The possible undesirable effects due to the use of Prilotekal are generally similar to the undesirable effects of other local anaesthetics for spinal anaesthesia from the amide group. The undesirable effects induced by the medicinal product are difficult to distinguish from the physiological effects of the nerve block (e.g. reduction in arterial pressure, bradycardia, temporary urine retention), from direct effects (e.g. spinal hematoma) or the indirect effects (e.g. meningitis) of the injection or from the effects due to the loss of cerebrospinal liquid (e.g. post-spinal headache).

The frequency of onset of undesirable effects is classified as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Methemoglobinemia, Cyanosis
Immune system disorders	Rare	Anaphylactic shock, Anaphylactic reactions, Allergic reactions, Itching
Nervous system Disorders	Common	Paresthesia, Dizziness
	Uncommon	Signs and symptoms of CNS toxicity (convulsions, circumoral paresthesia, loss of consciousness, shaking, feeling of numbness affecting the tongue, speech problems, hearing problems, tinnitus, visual problems)
	Rare	Arachnoiditis, Neuropathy, Lesions of peripheral nerves
Eye disorders	Rare	Diplopia
Cardiac disorders	Uncommon	Bradycardia
	Rare	Cardiac arrest, Arrhythmia
Vascular disorders	Very common	Hypotension
	Uncommon	Hypertension
Respiratory, thoracic	Rare	Respiratory depression

and mediastinal disorders		
Musculoskeletal and connective tissue disorders	Uncommon	Back pain, temporary muscle weakness
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting

The signs of intoxication from local anaesthetics are similar for any injected preparation, both in the way in which they manifest, and in their treatment. In spite of the demonstrated high clinical tolerability of Prilotekal, undesirable toxic effects cannot be excluded in the presence of plasma levels above a critical threshold. These undesirable effects mainly manifest as symptoms affecting the central nervous and cardiovascular system.

The most effective prophylactic measures are scrupulous compliance with the recommended posology for Prilotekal, with it being essential for the doctor to check its action (visual and verbal contact with the patient), as well as careful aspiration prior to injecting the solution.

Mild undesirable effects (feeling dizzy or dazed) can be attributed to moderate overdose and generally resolve rapidly after reducing the dose or halting administration of Prilotekal.

Serious undesirable effects are attributable to significant overdose and/or accidental injection of local aesthetic into a blood vessel. They manifest as symptoms affecting the central nervous system (restlessness, speech problems, disorientation, dizziness, muscle contractions, cramps, vomiting, loss of consciousness, respiratory arrest and mydriasis) and the cardiocirculatory system (raised arterial pressure and pulse frequency, arrhythmia, drop in arterial pressure, asystole) following irritation and/or depression of the cerebral cortex and the cerebral marrow (see section 4.9).

In addition, following inhibition or block of the cardiac conduction system, cardiac frequency may slow down and myocardial depression may occur.

Any problems relating to metabolism (liver) or excretion (kidney) of Prilotekal should also be considered as other possible causes of undesirable effects.

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 at: www.mhra.gov.uk/yellowcard

4.9 Overdose

It is unlikely that Prilotekal, at the recommended posology, will induce plasma levels capable of inducing systemic toxicity.

Acute systemic toxicity

Systemic undesirable effects, which may occur in the presence of plasma levels of more than 5-10 micrograms of prilocaine/ml, are iatrogenic, pharmacodynamic or pharmacokinetic origin and concern the central nervous system and the cardiocirculatory system. Iatrogenic undesirable effects occur due to:

- injection of an excessive quantity of solution
- accidental injection into a vessel
- incorrect patient position
- high spinal anaesthesia (marked drop in arterial pressure)

In the case of accidental intravenous administration, the toxic effect occurs within 1-3 minutes. On the contrary, in the case of overdose maximum plasma concentrations are only reached after 20-30 minutes, depending on the injection site, and the onset of signs of toxicity is delayed.

Signs of overdose can be classified into two different sets of symptoms which differ in terms of quality and intensity:

a) Symptoms affecting the central nervous system

Generally, the first symptoms are paresthesia in the mouth area, feeling of numbness of the tongue, feeling dazed, problems with hearing and tinnitus. Visual problems and muscle contractions are more severe and precede a generalized convulsion. These signs must not be erroneously mistaken for neurotic behaviour. Subsequently loss of consciousness and tonic-clonic seizure may occur, generally lasting between a few seconds and a few minutes. The convulsions are immediately followed by hypoxia and increased levels of carbon dioxide in the blood (hypercapnia), attributable to increased muscular activity associated with respiratory problems. In serious cases respiratory arrest may occur. Acidosis potentiates the toxic effects of local anaesthetics.

The reduction or improvement of symptoms affecting the central nervous system can be attributed to the redistribution of local anaesthetics outside the CNS, with its consequent metabolism and excretion. Regression may be rapid, unless enormous quantities have been used.

b) Cardiovascular symptoms

In serious cases cardiovascular toxicity may occur. Hypotension, bradycardia, arrhythmia and also cardiac arrest may occur in the presence of a high systemic concentration of local anaesthetics.

The first signs of toxic symptoms affecting the central nervous system generally precede toxic cardiovascular effects. This statement does not apply if the patient is under general anaesthesia or heavily sedated with medicinal products such as benzodiazepine or barbiturates.

Management of acute systemic toxicity

The following measures must be taken immediately:

- Stop administration of Prilotekal.
- Ensure an adequate supply of oxygen: keep the airways clear, administer O₂, artificial ventilation (intubation) if required.

In the event of cardiovascular depression circulation must be stabilized. If convulsions occur and do not resolve spontaneously after 15-20 seconds, the administration of an intravenous anticonvulsant is recommended.

Analeptics with a central action are contraindicated in the case of intoxication caused by local anaesthetics!

In the event of serious complications, when treating the patient it is advisable to obtain the assistance of a doctor specializing in emergency medicine and resuscitation (e.g. anaesthetist).

Methemoglobinemia

Methemoglobinemia may follow the administration of prilocaine. Prilotekal is contraindicated for techniques of regional anaesthesia requiring continuous administration. The doses used in subarachnoid anaesthesia do not induce blood levels capable of inducing methemoglobinemia, which occurs if the quantity of prilocaine hydrochloride administered is equal to or higher than 600 mg.

There is a metabolite of prilocaine, o-toluidine, which can induce methemoglobin formation. In general, methemoglobin formation is clinically negligible, except in cases of extremely severe anaemia and high grade cardiac decompensation.

Patients with severe anaemia may develop hypoxia. It is important to exclude other serious causes of cyanosis, e.g. acute hypoxia and/or cardiac insufficiency.

Management of methemoglobinemia

Proven methemoglobinemia resolves 15 minutes after the i.v. injection of 2-4 mg/kg body weight of toluidine blue.

Additional information:

Even low concentrations of methemoglobin can alter measurements of pulse oxymetry.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, local; amides

ATC code: N01BB04

Mechanism of action: Prilocaine is an amide-type local anaesthetic. Prilocaine inhibits the function of the excitable structures (e.g. all types of nerve fibres [sensory, motor, autonomous nerve fibres]).

Pharmacodynamic effects: Prilocaine inhibits the excitability of sensory pain receptors and the conductivity of the sensory nerve fibres, at local level and in a reversible way, reducing the perception of pain and, subsequently, that of cold, heat, touch and pressure.

Clinical efficacy and safety:

Prilocaine reduces membrane permeability to sodium. This reduces the excitability of the nerve fibres in accordance with its concentration, through reducing the sudden peak sodium permeability, needed to form the potential for action. The effect depends on the pH of the substance and the pH of the environment. The local aesthetic effect is due to the protonated form. In inflamed tissues, the effect of the local anaesthetics is lower because of the lower pH of the environment.

5.2 Pharmacokinetic properties

Absorption and Distribution

The plasma concentration should be negligible for intrathecal use.

Biotransformation and Elimination

The plasma protein binding is approximately 55%.

The bioavailability of prilocaine at the application site is 100%.

The principal metabolites of prilocaine are o-toluidine and N-n-propylalanine, both produced in the liver and kidneys by amidases. o-Toluidine undergoes extensive hydrolytic metabolism in vivo, with the bulk of the dose being excreted in the urine within 24 h. Like other aromatic amines, it is thought to undergo metabolic activation initially via N-hydroxylation, leading to covalent binding to tissue macromolecules. o-Toluidine is potent oxidant of the ferric iron of hemoglobin.

The terminal elimination half-life of prilocaine is 1.6 hours.

5.3 Preclinical safety data

The therapeutic dose used locally in humans is close to the dose which is toxic in animals after intravenous administration. In animals, signs of acute toxicity are reduced activity, convulsions, dyspnea, cyanosis and death on account of cardiac insufficiency.

The subcutaneous injection of 3 ml/kg of body weight of prilocaine hydrochloride induced reversible local necrosis in the rat. At the same posology no damaging effects were observed in the monkey.

The administration of 60 mg/kg body weight of prilocaine for 5 days a week for 7 weeks induced slight weight loss in the rat.

In mutagenesis tests, prilocaine did not demonstrate any mutagenic effects. The indices for a potential mutagen are based on knowledge relating to the metabolite o-toluidine, which caused genetic damage and cell proliferation (chromosome mutations, aneuploidy, DNA repair, cell conversion) in various tests *in vitro*.

In carcinogenicity studies performed in the rat and the mouse with high doses of the metabolite o-toluidine, an increase in the frequency of tumours of the spleen and the bladder were observed.

Neither of the results seem significant for humans in the case of the therapeutic short-term use of prilocaine; nevertheless, for safety reasons avoiding the administration of high doses over prolonged periods is recommended.

Prilocaine has no effect on the fertility of male and female rats. However, the postnatal survival of the offspring of treated females was reduced. In one study on embryotoxicity in the rat lethal effects on the foetus were observed, and dose-dependent hydronephrosis occurred in the foetuses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose anhydrous or glucose monohydrate

Sodium hydroxide 1N (for pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

The medicinal product has to be used immediately after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.

Store in original package in order to protect from light.

6.5 Nature and contents of container

Type I clear colourless glass ampoule

Box of 10 ampoules each containing 5 ml of solution for injection

6.6 Special precautions for disposal

5 ml ampoules of solution for injection are exclusively single-use.

Any remaining product must be disposed of.

The medicinal product has to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 03551/0163

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28/12/2022