

Takiprii®

20 mg/ml solution for injection
prilocaine hydrochloride

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 and mediastinal disorders	Rare	Respiratory depression
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 Takipril, 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 Takipril, 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 Takipril. Serious undesirable effects are attributable to significant overdose and/or accidental injection of local anaesthetic into a blood vessel. They manifest as symptoms affecting the central nervous system (restlessness, speech problems, dis-orientation, 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 Takipril 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 national reporting system.

4.9 Overdose

It is unlikely that Takipril, 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 Takipril.
- 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. Takipril 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 pulsoxymetria.

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 anaesthetic 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 hydro-nephrosis 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

2 years

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

6.4 Special precautions for storage

Do not store above 30°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

Not all presentations may be available locally

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 authorization holder

B. Braun Singapore Pte Ltd

600 North Bridge Road

#15-05 Parkview Square

Singapore 188778

8. Batch released by

Sintetica SA

Via Penate 5

CH-6850 Mendrisio

Switzerland

9. Date of revision of the text

June 2020