sp.zn. sukls245088/2018

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Injectio trimecainii chlorati Ardeapharma 0,5% solution for injection
Injectio trimecainii chlorati Ardeapharma 1% solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injectio trimecainii chlorati Ardeapharma 0,5%

One ml of solution for injection contains trimecaini hydrochloridum 5 mg.

The amount of active substance in volume:	80 ml	250 ml	500 ml
Trimecaini hydrochloridum (0.5%)	400 mg	1250 mg	2500 mg

Excipients with a known effect:

One ml of solution for injection contains 3.09 mg of sodium.

Injectio trimecainii chlorati Ardeapharma 1%

One ml of solution for injection contains trimecaini hydrochloridum 10 mg.

The amount of active substance in volume:	80 ml	250 ml	500 ml
Trimecaini hydrochloridum (1%)	800 mg	2500 mg	5000 mg

Excipients with a known effect:

One ml of solution for injection contains 2.60 mg of sodium.

For the full list of excipients, see the section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Description of the product: clear, colorless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

All types of local anesthesia, especially infiltration, surface or conduction anesthesia.

As a part of cardiopulmonary resuscitation or complex therapy of recurrent persistent ventricular tachycardia or ventricular fibrillation, when beta-blocker or amiodarone or trimecaine is usually administered (especially, but not only in case of contraindication of amiodarone or no response after the administration of beta-blockers or amiodarone).

4.2. Posology and method of administration

a) The use for local anesthesia, commonly recommended doses

Surface anesthesia

Solution 1% is used for surface anesthesia in ophthalmology.

Infiltration anesthesia

Solution 0.5% - 1% is used for infiltration anesthesia.

Maximum doses for infiltration anesthesia:	solution 0.5%	150 ml/day
	solution 1.0%	50 ml/day

In case of need, the required amount of solution of Injectio trimecainii chlorati Ardeapharma (0.5% or 1%) can be diluted with isotonic solution of sodium chloride to a demanded concentration.

Conduction anesthesia

Solution 1% is used for conduction anesthesia (up to 50 ml/day).

Pediatric population

Local anesthesia in children

Doses of anesthetic are the same as those in adult patients using a relevant recalculation for a lower body weight having in mind that the as low as possible effective concentration is necessary to be used. Maximum recommended dose is 7 mg of trimecaine/kg of body weight with addition of adrenaline (1: 200 000) or 4.5 mg/kg without addition of adrenaline. In children, conduction anesthesia can be applied from the age of about 3 – 4 years. Each time, it is necessary to judge individually whether the child is able to manage such type of procedure.

b) The use in therapy and prophylaxis of ventricular tachycardia or ventricular fibrillation

In case of ventricular tachycardia, 50 – 200 mg (1.0 – 1.5 mg/kg) is administered i.v. slowly (during 2 – 3 minutes) according to the individual patient's condition. If no effect on tachycardia comes, then it is possible to repeat the dose in 3 – 5 minutes up to the total dose 3 mg/kg. After that, a long-term infusion follows at the rate of 1.5 - 4 mg/min according to the patient's response. Not to exceed the duration of the infusion over 12 hours (toxic dose).

In cardiopulmonary resuscitation in cases of repeated ventricular fibrillation, the dose 1 mg/kg of body weight is administered i.v. before the repeated defibrillation.

As a prophylaxis during the transport of the patient suffering from myocardial infarction or as a prevention of serious arrhythmias and early ventricular fibrillation within the first 24 hours in acute myocardial infarction, trimecaine in form of either i.v. bolus 50 – 80 mg or the infusion 3 – 4 mg/min is possible to be administered, alternatively 250 – 300 mg of trimecaine (25 – 30 ml of solution 1%) can be applied i.m.

Pediatric population

Antiarrhytmic dosage in children

The initial dose 1 mg/kg i.v. bolus (no more than 100 mg/dose). If the infusion administration is not initiated within 15 minutes, then another i.v. bolus as a dose 0.5 - 1 mg/kg is possible to be administered. As such repeated i.v. bolus, maximum 3 – 5 mg of trimecaine/kg can be administered, then the therapy continues with the infusion application of 8 – 50 μg/kg/min.

c) Posology in special populations

Elderly people

Lower doses and a slower infusion rate are necessary to be used in individuals aged 65 years or older; in ventricular tachycardia, the infusion only 2 mg/min.

Patients with liver function disorder

In patients with a severe liver function disorder, especially in hepatic cirrhosis, lower doses and slower infusion rate are necessary to be used.

Patients with impaired renal functioning

In impaired renal functioning, the doses are not to be changed.

Lowe doses and slower infusion rate must be used:

- in cardiogenic shock, atrial arrhythmias, in AV blocks
- in mild congestive heart failure (major doses can provoke serious hypotension), in patients with serious congestive heart failure, we choose only a half-dose as an initial dose and a slower infusion rate
- it can be used with caution in hemodynamically stabile pregnant women

4.3. Contraindications

Hypersensitivity to the medicinal substance or other amide local anesthetics, asystolia, bradycardia, atrial dysrhythmia, atrioventricular blocks, cardiogenic shock, hypovolemia, hypotension, porphyria, malign hyperthermia in medical history.

4.4. Special warnings and precautions for use

In case of overdose or also in incorrect intravasal administration of the dose, toxic reaction is developed.

Allergic reaction can be developed after the administration in sensitive persons.

Events of ventricular tachycardia in children are relatively frequent and trimecaine in such cases is effective even in children (including cases of idiopathic ventricular tachycardia).

Systemic toxicity (for central nervous system, cardiovascular) of trimecaine in children is higher and children are also at a higher risk of complications, namely regarding children younger than one year. Therefore, an increased attention should be paid with the use of trimecaine.

Major attention should be paid in children also with the use of trimeacine for local anesthesia or epidural anesthesia.

Injectio trimecainii chlorati Ardeapharma 0,5%

One ml of solution for injection contains 3.09 mg of sodium, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Injectio trimecainii chlorati Ardeapharma 1%

One ml of solution for injection contains 2.60 mg of sodium, equivalent to 0,1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. Interaction with other medicinal products and other forms of interaction

Major doses of the product may lead to an increase in efficacy and toxicity of antiarrhythmics, cardiotonic drugs, vasodilators and antihypertensives and may potentiate negatively inotropic effect of beta-blockers. Trimecaine plasma levels are increased by beta-blockers, cimetidine or halothane, and decreased by barbiturates, phenytoin and rifampicin. Local anesthetic effect is also decreased by glucose, calcium and vasodilators.

Drugs inducing hypokalemia cause a decrease in antiarrhythmic effect of trimecaine; propranolol causes a decrease in plasmatic clearance of trimecaine by reducing the liver flow rate; glucagon, isoprenaline and phenobarbital cause an increase in elimination of trimecaine by augmenting the liver flow rate.

There is no interaction with heparin effects.

Combinations of trimecaine with bupivacaine, with opioids from fentanyl group, with alfa-2 antagonists such as clonidine etc. are used for the acceleration of the effect onset and for prolonged effect as well as multifactorial action for local anesthesia, especially for the spinal anesthesia.

4.6. Fertility, pregnancy and lactation

There are not available sufficient epidemiologic data on the safety of trimecaine during gravidity and lactation. With regard to the fact that it goes through the placenta, it is recommended to consider the ratio of potential undesirable effects to the benefits from the use of the product. In case of the administration, it is recommended to reduce the dose. However, based on the experience, it seems that the risk of occurrence of congenital malformations in children delivered by mothers treated with trimecaine during the pregnancy is low.

Since trimecaine is excreted into breast lac, it is recommended to consider the ratio of potential undesirable effects to the benefits from its use. In case of administration, it is recommended to reduce the dose.

4.7. Effects on ability to drive and use machines

With regard to potential undesirable effects on central nervous system and cardiovascular effects, it is not recommended to perform activities attention-demanding.

4.8. Undesirable effects

Undesirable effects are classified after the classes of organ systems according to MedDRA database. They are classified for all organ system class according to the following convention:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be established from the available data).

Organ system class according to MedDRA database	Undesirable effect	Frequency of occurrence
Nervous system disorders	Tremor, coma, spasms, somnolence, hyporeflexia, metallic taste in mouth, nystagmus	rare
Psychiatric disorders	Excitation, restlessness, confusion, logorrhea	rare
Cardiac disorders	Hypotension, circulation arrest	rare
Ear and labyrinth disorders	Tinnitus	rare
Eye disorders	Vision disorders	rare
Respiratory, thoracic and mediastinal disorders	Irregular breathing, apnoea	rare
Immune system disorders	Anaphylactic shock, allergic reaction - dermal and mucosal	rare
General disorders and administration site conditions	Burning sensation, erythema at application site	rare

In case of incorrect intravasal administration of the dose intended for extravasal local anesthesia, toxic reaction is developed. The intensity of such reaction is closely dependent on the size of the dose administered. The symptoms such as those from the central nervous system, myocardium, haemodynamics: excitation, restlessness, logorrhea, mild confusion, vision disorders, tinnitus, metallic taste in mouth, nystagmus, shivering or even tremor of the limbs dominate. In case of severe reaction, somnolence, hyporeflexia, coma, disorders of breathing or even apnoea, often accompanied with convulsions, are developed. However, the phase of excitation and convulsions can be completely absent. Rapid loss of consciousness and acute circulation arrest are not exceptional events.

Allergic reactions are rare. The most frequent symptoms of allergic reaction include a development of anaphylactic shock or dermal and mucosal symptoms. The therapy of allergic reactions is the same as the therapy applied in anaphylactic events in general: elevated position of the lower limbs, volume supplementation, vasopressors, glucocorticoids, antihistaminic drugs, calcium, oxygen inhalation.

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 to the address:

Státní ústav pro kontrolu léčiv (State Institute for Drug Control)
Šrobárova 48
100 41 Praha 10

Website: www.sukl.cz/nahlasit-nezadouci-ucinek

4.9. Overdose

Disproportionately high doses of trimecaine can have toxic effects on CNS, peripheral nervous system and cardiovascular system. The symptoms of overdose are the same as undesirable effects as well as the therapy of such symptoms:

Mild excitation conditions respond favourably to diazepam i.v. In addition, in serious cases of spasms, muscle relaxation with artificial pulmonary ventilation is indicated. Hypotension responds favourably to supplementation of circulating volume via rapid infusion, to ephedrine, or else to dihydroergotamine as a single administration or dopamine infusion. In case of acute cardiac arrest, cardiopulmonary resuscitation is initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Local anesthetics, amides. ATC code: N01BB

Transmembrane ionic gradients on membrane interfaces are maintained by the sodium pump. Analogous processes take place on membranes of myocardial cells. Functioning of sodium channels is influenced by local anesthetics that are bonded to receptors near intracellular channel opening and block the channel depending on the time and voltage value. If local anesthetic is applied to a nervous fibre, then the threshold for excitation is increased, conduction of impulses is slowed down. All of these effects are caused by the bond of local anesthetic to sodium channels. If sodium current is blocked in the segment of the nerve which exceeds a certain critical length, the propagation of the impulse through such blocked area is not possible.

An increase in extracellular calcium partially antagonizes the effect of local anesthetics. On the contrary, an increase in extracellular potassium causes a depolarization of membrane potential and facilitates the development of inactivated state. Thus the effect of anesthetics is augmented. Trimecaine belongs to amide local anesthetics. In comparison with procaine, trimecaine has approximately double effectivity and with regard to the fact that trimecaine does not belong to the same chemical group as procaine, it has no cross allergy with procaine.

5.2. Pharmacokinetic properties

a) Chemical structure of local anesthetics consists of lipophilic group (aromatic nucleus) on one side, and ionisable ending on the other side. Both ends of trimecaine molecule are connected by the chain containing amide group. The effect is generally dependent on the ratio of water solubility/fat solubility. Certain water solubility is necessary for diffusion into tissues, fat solubility is important for interaction with the receptor. The solubility depends also on pH of the environment. The level of ionisation is the explanation for experience that a low efficacy in inflammatory tissue, where lower pH causes an increase in ionisation, exists.

b) Biotransformation takes place in the liver where trimecaine is metabolized and then is excreted by kidneys, namely 10 % as unchanged form and 90 % in form of metabolites. Biological half-time is approximately 90 minutes. A major reduction of liver functioning by some pathological process can result in a significant prolongation of biological half-time. The medicinal substance crosses hematoencephalic and placental barriers. Acidic pH of tissue in inflammation reduces its efficacy, while alkalemia causes a moderate increase in its action.

c) Anesthetic effect starts within 15 minutes after the administration and lasts for 60 – 90 minutes. The addition of adrenalin to the solution in the dose 1: 200 000 increases the therapeutic index, and thus also a single-time maximum dose.

5.3. Preclinical safety data

Acute toxicity (LD_{50}) of trimecaine hydrochloride in mice is about 50 mg/kg i.v., 295 mg/kg s.c., 172 mg/kg i.p., in rabbits cca 95 mg/kg i.p. and in rats cca i.m. 450 mg/kg i.m.. Neither special toxicological study nor reproductive toxicity trials have been done; one of the metabolites (trimethylaniline), however, shows genotoxic effects.

6. PHARMACEUTIAL PARTICULARS

6.1. List of excipients

Sodium chloride

Water for injection

6.2. Incompatibilities

In indications, where the product of Injectio trimecainii chlorati Ardeapharma is used, only vasoconstrictive substances are used as an additive. In cases of their use, no physical and chemical incompatibilities have been known.

6.3. Shelf life

1 year provided that the package is intact.

Chemical and physical stability before the use after the opening was confirmed for 48 hours at 25°C.

Chemical and physical stability after the dilution with isotonic solution of sodium chloride was confirmed for 24 hours at 25 °C.

From microbiological point of view, the product should be used immediately. If it is not used immediately, then the period and storage conditions of the product after the opening before the use are within the reliability of the user and in common case it should not be longer than 24 hours at 2-8 °C provided that the opening/dilution was not performed under the controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store the bottle in the box to protect the product from light. Protect from frost.

6.5. Nature and contents of container

Infusion glass bottle with a rubber stopper and a metallic closure.

Package size: 1x 80 ml, 1x 250 ml, 1x 500 ml

10x 80 ml, 20x 80 ml, 10x 250 ml, 10x 500 ml

Not all package sizes may be marketed.

6.6. Special precautions for use, disposal and other handling

This medicinal product is dispensed entirely on the base of medical prescription.

Parenteral products should be checked up visually before the use. The product must not be administered if visible solid particles are present or the package is not intact.

The preparation is intended only for a single use.

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

7. MARKETING AUTHORISATION HOLDER

ARDEAPHARMA, a.s., Třeboňská 229, 373 63 Ševětín, Česká republika (Czech Republic)

8. MARKETING AUTHORISATION NUMBER(S)

Injectio trimecainii chlorati Ardeapharma 0,5%: 01/229/95-A/C

Injectio trimecainii chlorati Ardeapharma 1%: 01/229/95-B/C

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorization: 19th April 1995

Date of the last renewal of the authorization: 4th May 2016

10. DATE OF REVISION OF THE TEXT

10th August 2018