**sp.zn. sukls245088/2018**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**Injectio procainii chlorati Ardeapharma 0,2%** solution for injection

**Injectio procainii chlorati Ardeapharma 0,5%** solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injectio procainii chlorati Ardeapharma 0,2%

One ml of solution for injection contains procaini hydrochloridum 2 mg.

| The amount of active substance in volume: | 80 ml | 200 ml | 250 ml | 500 ml |
|---|---|---|---|---|
| Procaini hydrochloridum (0.2%) | 160 mg | 400 mg | 500 mg | 1000 mg |

Excipients with a known effect:

One ml of the solution for injection contains 3.38 mg of sodium.

Injectio procainii chlorati Ardeapharma 0,5%

One ml of the solution for injection contains procaini hydrochloridum 5 mg.

| The amount of active substance in volume: | 80 ml | 200 ml | 250 ml | 500 ml |
|---|---|---|---|---|
| Procaini hydrochloridum (0.5%) | 400 mg | 1000 mg | 1250 mg | 2500 mg |

Excipients with a known effect:

One ml of the solution for injection contains 3.07 mg of sodium.
The medicinal product contains sodium disulphite.

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

## 3. PHARMACEUTICAL FORM

Solution for injection

Description of the product: clear, colourless or slightly yellowish solution

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Local infiltration anesthesia, conduction anesthesia of thin nerves, intravenous analgesia.

### 4.2. Posology and method of administration

***Intravenous analgesia:*** the dose 50 - 100 mg of procaine is usually administered. The therapeutic dose for intravenous application (50 - 100 mg) is suitable to be administered after a dilution by physiological solution under aseptic conditions for concentration 0.1 – 0.25 %. For dilution, both solutions of original concentrations can be used. Concentration 0.2 % (the solution also diluted as given above) may also be administered via intravenous infusion in the closed system. Total dose should not exceed 200 mg of procaine. Doses 450 mg of procaine or higher are toxic.

***Local infiltration anesthesia:*** usually, dose 50 - 100 mg of procaine is administered; within one procedure, doses up to 600 mg of procaine can be administered, i.e. up to 300 ml of the solution

having concentration 0.2 % or up to 120 ml of the solution 0.5 %. Both concentrations can be used or a higher concentration can be diluted under aseptic condition for required concentration. The dose is individual and its amount is dependent on the extent of the procedure (it is usually used in minor interventions), reactivity of the patient and blood perfusion of the area. The as low as possible dose and concentration needed for achievement of required effect is used. The total dose is administered in fractionated way with gradually increasing doses; for infiltration, it is proceeded from superficial and undersurface structures to the tissues located deeper. Various methods of application can be used ranged from intradermal and subcutaneous or submucosal administration (in tolerable volumes) to intramuscular or intratissual administration or into surroundings of the wound or into the wound directly. Injections should be applied slowly with repeated aspirations to prevent intravenous application. Maximum cumulated total dose of procaine for one procedure is 7 mg/kg; the total dose should not be higher than 350-600 mg.

Doses for children:

As a one-time application: 3 - 5 mg/kg in solution 0.5% within l hour; it cannot be repeated for another 2 hours. Maximum recommended dose in children is 15 mg/kg in solution 0.5% in infiltration anesthesia.

***Conduction anesthesia of thin nerves:*** usually, dose 50 - 100 mg of procaine is aministered; it can be administered up to 500 mg of procaine in oneprocedure, i.e. up to 100 ml of the solution with concentration 0.5 %. The higher concentration is preferred. However, it can be diluted under aseptic conditions for a suitable lower concentration. Total dose is mostly administered in fractionated way via perineural application. Daily cumulated dose must not exceed 1000 mg of procaine.

Special groups of patients
Doses of procaine should be lowered appropriately in elderly or weakened patients (by 10 – 20 %). In patients with impaired renal functions, the dose of procaine should be lowered by 10 - 20 % depending on the level of impairment when high doses are planned or in the application via infusion. In patients with impaired liver functions, the dose also should be lowered by 10 – 50 % depending on the level of impairment in case of repeated application or the administration by infusion. In patients with major level of cardiac failure, the dose of procaine should be lowered by 10 – 20 % when administered repeatedly or by infusion.

Method of administration: intradermal, subcutaneous, intramuscular, intravenous. Concentration 0.2 % (also a solution diluted as given above) as an intravenous infusion in the closed system.

The product is intended for a single use. Any waste should be disposed of.

The product of Injectio procainii chlorati Ardeapharma can be used independently on taking food and drinking.

**4.3. Contraindications**

- hypersensitivity to the medicinal substance or any of the excipients given in the section 6.1
- hypersensitivity to other local anesthetics of ester-type
- parallel therapy with sulphonamide preparations
- cardiac decompensation
- especially the intravenous administration is contraindicated in major diseases of liver or kidney diseases, in hypothyreosis, myasthenia gravis, serious shock condition and in hypotension.

**4.4. Special warnings and precautions for use**

Toxic reaction may be developed in sensitive individuals if administered incorrectly intravenously or intraarterially.

If the patient suffers at the same time from any of the following conditions: non-compensated epilepsy, infection or inflammation at the application site, deficiency or lowered levels of plasma

pseudocholinesterase, then the product containing procaine should be administered only in well-founded cases.

Local anesthetics should be administered in departments with sufficient personal capacity and material equipment. If a higher dose of local anesthetic is needed to be administered into sites with sufficient blood perfusion, then the risk of toxic reaction is increasing. Therefore, oxygen and other drugs and equipment for urgent resuscitation must be ensured. A delayed response to developing toxicity, hypoventilation and impaired sensitivity can lead to acidosis development, cardiac arrest or even to death.

If it is possible, a slow fractionated administration of procaine should be preferred to a rapid bolus as an injection. Before the initial injection as well as the other repeated injections, aspiration is necessary to be performed as a prevention of intravascular administration of anesthetic. However, in spite of applying this procedure, the danger of intravenous administration is not excluded completely.

In patients with impaired liver function, cholinesterase plasma levels can be decreased. In such group of patients, a higher risk of the development of toxic reaction exists, especially if higher doses of ester type local anesthetic are administered repeatedly.

Special caution should be exercised in patients suffering from serious disorder of cardiac conduction system functioning due to potential influence on electrical signal conduction. Such patients have a decreased ability to compensate changes of function caused by prolongation of AV conduction in procaine administration.

Proper and constant monitoring of cardiovascular and respiratory parameters, life functions and consciousness condition of the patient should be carried out after each administration of anesthetic. It is necessary to be aware of the fact that symptoms such as restlessness, anxiety, incoherent speech, vertigo, numbness and tingling of mouth and lips, metallic bad taste, tinnitus, blurred or not sharp vision, tremor, crispation, depression or somnolence can be early symptoms of neurotoxicity.

In case of muscle stiffness symptoms (in masticatory muscles first), tachycardia, tachypnoea, blood pressure fluctuations and metabolic acidosis after the application of local anesthetic, the risk of occurrence of malign hyperthermia should be taken into account.

In case of spasms or allergic reaction occurrence, the adequate therapy is necessary to be commenced (see the sections 4.8 and 4.9).

Injectio procainii chlorati Ardeapharma 0,2%

One ml of the solution for injection contains 3.38 mg of sodium, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Injectio procainii chlorati Ardeapharma 0,5%

One ml of the solution for injection contains 3.07 mg of sodium, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The medicinal product with concentration 0.5% contains sodium disulphite that can provoke severe allergic reactions and bronchospasm.

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

Procaine hydrochloride causes an increase in the effectivity and toxicity of antiarrhythmics, vasodilators, peripheral muscle relaxants. Its toxicity is decreased by drugs having vasoconstrictive effect (e.g. epinephrine). Its toxicity is increased by cholinesterase inhibitors, morphine, ephedrine. Procaine hydrochloride forces out sulphonamides from the bond, and thus devalues the effect of sulphonamides.

## 4.6. Fertility, pregnancy and lactation

Pregnancy

If the dose lower than 4 mg/kg is administered to a pregnant woman, procaine does not penetrate into foetal blood at all, because it is earlier decomposed.

Breast-feeding

There has been no sufficient information on the use of procaine during lactation. With regard to low breast lac levels of other local anesthetic, a low partition coefficient as well as to a short procaine half-time, it is improbable that the breast-fed child could be influenced negatively, with the exception of a new-born or premature baby. Some sources have reported about the procedure with a short-term interruption of breast-feeding and its repeated start in 4 hours after the application of procaine.

Fertility

There are no known studies on procaine influence on fertility either in men or women.

### 4.7. Effects on ability to drive and use machines

It is not recommended to carry out activities demanding close attention after the administration of products with procaine, until a potential lower level of attention fades away. A decrease in attention can be caused not only by the application of the product itself but also by an anxiety response to the surgical procedure. In any case, the physician must separately decide, whether the patient may actively take part in road traffic or use machines and tools. After minor, short, local interventions, the driving is possible to be permitted in about 4 hours after the procaine application; after long-term interventions with use of higher doses of procaine and repeated application of such doses, it is advisable to wait overnight (with regard to post-operative condition of the patient, of course).

### 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** | Shivering of limbs, coma, spasms, hyporeflexia | rarely |
| **Psychiatric disorders** | Excitation, restlessness | rarely |
| **Cardiac disorders** | Decrease in blood pressure, circulatory failure | rarely |
| **Ear and labyrinth disorders** | Tinnitus | rarely |
| **Gastrointestinal disorders** | Nausea | rarely |
| **Respiratory, thoracic and mediastinal disorders** | Irregular breathing, tachypnoea | rarely |
| **Immune system disorders** | Anaphylactic shock, allergic reaction - dermal and mucosal | rarely |
| **Skin and subcutaneous tissue disorders** | Urticaria, itching, erythema, angioneurotic edema | rarely |

Allergic reactions are rare and non-dependent on the dose. The most frequent symptom of that is anaphylactic shock development or dermal and mucosal symptoms. In case of allergic reaction, the procedure is similar to that in anaphylactic events: adrenaline, volume supplementation, glucocorticoids, antihistaminic drugs, oxygen inhalation and elevated position of the lower limbs.

Cardiovascular toxicity occurs usually with high plasmatic levels of local anesthetics. In rare cases, even a small amount of anesthetic used in infiltration can cause cardiovascular collapse. In case of toxic reaction onset, circulatory failure, hypotension, coma or sometimes also spasms ranged from sporadic crispation to generalized tonic-clonic spasms, hyporeflexia with irregular breathing can

occur. The patient should be converted to controlled ventilation, treated with peripheral analeptics as required, or with benzodiazepines in case of spasms.

**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

High procaine plasma levels in overdose have an influence preferably on central nervous system (CNS) and cardiovascular system. In most cases, first stimulation of CNS manifested by symptoms such as anxiety, anxious ideas, restlessness, nervousness, disorientation, confusion, vertigo, blurred or not sharp vision, tremor, crispation, shivering and spasm seizures occur. These symptoms are followed by repression of CNS with symptoms such as somnolence, coma or breath arrest. Nausea, vomiting, cold-bloodedness, miosis and tinnitus can also be observed. The excitation phase of neurotoxicity may not be marked out, the repression of CNS can be expressed directly.

Toxic cardiovascular effects are manifested by depression of myocardium, bradycardia with prolonged PR interval and widened QRS complex, cardiac arrhythmia, hypotension, tachycardia, ventricular fibrillation, cardiovascular collapse or heart arrest. An early symptom of cardiotoxicity usually is the occurrence of high spiked T waves on ECG. Although cardiovascular toxicity occurs usually with high plasma levels of local anesthetics, in rare cases even a small amount of the anesthetic used for infiltration can cause cardiovascular collapse.

In case of symptoms of acute toxicity, the intake of local anesthetic is necessary to be stopped immediately.

In case of overdose and occurrence of spasms, an adequate therapy should be necessarily initiated as soon as possible. Oxygen inhalation, suppression of spasms by administration of diazepam or midazolam and support of systemic circulation belong to main principles of the therapy. In serious convulsions, muscle relaxation with artificial ventilation is needed to be ensured.

In case of acute circulation arrest, cardiopulmonary resuscitation according to given procedures should be started. Similarly as in CNS toxicity, the therapy is supportive: oxygen, fluids, vasopressors, inotropic substances and antiarrhythmics are administered as needed.

Hypotension could be adjusted by blood volume supplementation via rapid infusion and administration of vasopressors.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Local anesthetics, esters of aminobenzoic acid, ATC code N01BA02

Transmembrane ionic gradients on membrane interfaces are maintained by the sodium pump. 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.

### 5.2. Pharmacokinetic properties

Procaine hydrochloride is soluble in water very easily, while solubility in ethanol is worse, and is practically insoluble in non-polar organic solvents.
Procaine hydrochloride injection is usually applied in proximity of such nerve fibres that should be blocked in either infiltration or conduction anesthesia. The other indication is intravenous analgesia where procaine hydrochloride is applied intravenously. From the application site (under skin or from tissues around nerve fibres), procaine is relatively rapidly distributed into surroundings and absorbed into circulation. Vasoconstrictive substances such as adrenaline cause a decrease in procaine absorption from the application site. Plasma protein binding is low, it fluctuates around 6 %. Procaine hydrochloride is a local anesthetic with ester bond, and that is why it is easily subjected to hydrolyse by maternal or foetal plasma cholinesterase. Procaine goes through placental barrier (with regard to rapid hydrolyse, however, only in small amounts) and is also excreted (probably in a minor amount) into breast-milk. Procaine is relatively rapidly split by plasma cholinesterases into para-aminobenzoic acid (PABA) and diethylaminoethanol. Approximately 80 % of para-aminobenzoic acid is eliminated by urine (both free and conjugated), approximately 20 % is further metabolized in the liver. Approximately 30 % of diethylaminoethanol is eliminated by urine, the rest is metabolized in the liver. The elimination half-life of procaine is within a few minutes.

### 5.3. Preclinical safety data

Disproportionately high doses of procaine hydrochloride can have a toxic effect on CNS, peripheral nervous system and cardiovascular system.

## 6. PHARMACEUTIAL PARTICULARS

### 6.1. List of excipients

Sodium chloride

Sodium disulphite (only in Injectio procanii chlorati Ardeapharma 0,5%)

Hydrochloric acid l mol/l

Water for injection

### 6.2. Incompatibilities

In indications, where the product of Injectio procainii 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.

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 200 ml, 1x 250 ml, 1x 500 ml
20x 80 ml, 10x 200 ml, 10x 250 ml, 10x 500 ml

Not all package sizes may be marketed.

### 6.6. Special precautions for use, disposal and other handling

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.

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

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 procainii chlorati Ardeapharma 0,2%: 01/230/95-A/C

Injectio procainii chlorati Ardeapharma 0,5%: 01/230/95-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: 24th June 2015

## 10. DATE OF REVISION OF THE TEXT

10th August 2018