

sp.zn. suks156727/2010

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ardeaelytosol conc. L-argininchlorid 21% concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of concentrate for solution for infusion contains arginini hydrochloridum 210.0 g.

Electrolyte content:

Argininum⁺ 1000 mmol/l

Cl⁻ 1000 mmol/l

Osmotic pressure: 4 821 kPa

pH: 5.2-6.8

Energetic content: 3604 kJ/l

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for infusion solution

Description of the preparation: clear, colourless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Severe metabolic alkalosis, especially with liver damage and in cases where sodium chloride or potassium chloride solutions are not suitable (e.g. in case of hypernatremia).

Acute therapy of hyperammonemia (without identified reason so far).

Hyperammonemia in hereditary disorders of urea (ornithine) cycle with the exception of the ARG1D type (arginase deficiency), where especially hyperargininemia is present.

The product is indicated for therapy in newborns, children and adults.

4.2. Posology and method of administration

Dosage in metabolic alkalosis:

Individually according to base excess: ml of the preparation = BE x 0.3 x kg.

Speed of administration approximately 2 ml/kg/hour.

Dosage and speed of administration in children is the same.

Dosage for acute treatment of hyperammonemia in case of not so far identified cause of its inception:

Children as well as adult patients.

As a part of complex therapy where also arginine hydrochloride is applied:

250-400 mg/kg (1.2-1.9 mmol/kg) in initial infusion during 90-120 minutes, maintenance dose then is 250 mg/kg/day (1.2 mmol/kg/day). L-karnitine is recommended to be added in dose of 100 mg/kg IV, hydroxocobalamin 1 mg IM/IV and biotin 10 mg IV/perorally.

Alternatively: L-arginine 300 mg/kg/day IV (1.42 mmol/kg/day), L-karnitine 200 mg/kg/ day IV.

Dosage in hyperammonemia in case of hereditary disorders of urea cycle:

Children as well as adult patients.

As a part of complex therapy where also arginine hydrochloride is applied:

For CPS1D, OTCD, ASSD and NAGSD: initial infusion during 90-120 minutes, 250 mg/kg (1.2 mmol/kg), maintenance dose then 250 mg/kg/day (1.2 mmol/kg/day).

For ASLD: initial infusion during 90-120 min, 200-400 mg/kg (0.95-1.9 mmol/kg), maintenance dose then 200-400 mg/kg/day (0.95-1.9 mmol/kg/day).

Dosage in special population groups:

No correction of dosage in patients with hepatic function disorders is needed.

A decrease in used dose and rate of flow can be taken into account in patients with renal function disorders, according to the severity of the disorder.

There is no sufficient experience with the need of dose modification in elderly patients (over 65) but it can be assumed that such adjustment is not required unless the higher age is connected with renal function disorder.

Method of administration:

Intravenous drop infusion in the closed system.

Appropriate amount of the preparation is diluted with carrying solution (glucose 5% or 10%) in the ratio 1:6 (alternatively in a higher ratio); in well-founded cases even a higher final concentration of arginine may be used but not higher than 10 %.

Considering the fact that especially the risk of the irritation of the vein near the application site is increasing with an increase of product concentration (as much as 3 % incidence with 10% concentration), the administration via central catheter is more suitable than the administration into peripheral vein.

4.3. Contraindications

Metabolic acidosis.

Hyperargininemia in case of severe hereditary metabolic disorder – argininemia caused by arginase deficiency (ARG1D), and also in case of lysine intolerance and dibasic aciduria.

4.4. Special warnings and precautions for use

When L-arginine chloride is administered, serum potassium levels should be monitored because hyperkalemia may occur.

With the product administration, urea or creatinine serum levels can be increased, and that is why, especially in patients with renal function disorders or anuria, caution is necessary together with appropriate urea and creatinine serum levels monitoring. In patients suffering from serious renal function disorders or anuria, hemodialysis or hemo(dia)filtration should be taken into account.

Special attention should be paid to the dosage control and the administration of the preparation in children (often of a very early age); in children an increased rate of overdose may occur.

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

So far there has been found a minimal amount of clinically confirmed interactions.

The interaction with potassium-sparing diuretics may be clinically serious because both remedies can cause hyperkalemia and co-administration of both of them increases that risk notably.

With regard to a hypotensive effect of arginine, interaction with other substances with hypotensive effect can be assumed.

4.6. Fertility, pregnancy and lactation

The use of the preparation during gravidity or lactation is not contraindicated in such case where no other remedy to adjust acid-base balance can be used. The medicinal substance goes through the placental barrier.

No data on the product influence on fertility are available.

4.7. Effects on ability to drive and use machines

With regard to the characteristic of the product and its indication is not relevant.

4.8. Undesirable effects

Frequencies of undesirable effects given below are defined using the following convention:

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

Organ system class according to MedDRA database	Undesirable effect	Frequency of occurrence
Metabolism and nutrition disorders	- hyperkalemia	not known
	- hyperuremia	not known
	- ion balance breakdown	not known
	- metabolic acidosis	not known
Gastrointestinal disorders	- nausea	not known
	- vomiting	not known
Heart disorders	- hyperhydration	not known
	- swelling	not known
Nervous system disorders	- headache	not known
	- cerebral oedema	not known
Immune system disorders	- anaphylactoid reaction	not known
Muscular, skeletal or connective tissue disorders	- sensitivity decrease (in limbs)	not known
	- tingling or pinching sensation around mouth	not known
Vascular disorders	- reddening (flushing)	not known
	- hypotension	not known
Skin and subcutaneous tissue disorders	- rash	not known
	- oedema	not known
General disorders and reactions on the application site	- burning sensation or pain on the application site	not known
	- necrosis of surrounding tissue on the injection site in case of extravasation	not known

The higher concentration or rate of arginine infusion flow is, the higher the incidence of some undesirable effects is.

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

In the event of overdose, hyperkalemia can occur. The state of homeostasis of the organism should be monitored. If metabolic acidosis is concurrently present, the adjustment of both conditions by means of bicarbonate is suitable. Otherwise hyperkalemia can be adjusted in different ways depending on its suitability – IV calcium, ionexchanger Calcium Resonium, furosemide with saline solution, insulin with glucose, inhaled salbutamol or terbutaline or hemodialysis.

The overdose may also result in (especially in children) metabolic acidosis with hyperventilation, cerebral oedema even with fatal ending. Metabolic acidosis usually subsides after finishing the application of arginine hydrochloride. In case of its persistence, it can be adjusted by relevant amount of alkalizing substance such as sodium bicarbonate.

Other symptoms of overdose should be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: IV solution additive, amino acids, arginine hydrochloride, ATC code: B05XB01.

Arginine belongs to so called semi-essential (conditionally-essential) amino acids which means those that the adult organism can synthesize itself but under certain circumstances the synthesis is not sufficient (growth, convalescence or some diseases) and should be supplemented by the nourishment. Metabolic alkalosis can arise from a few various reasons. The following ones can be taken into account: hypochloremic metabolic alkalosis caused by excessive loss of gastric juices (e.g. vomiting), thiazide diuretics, diarrhea, etc.; hypokalemic metabolic acidosis caused e.g. by primary aldosteronism, some drugs (laxatives, liquorice...) or congenital tubulopathies (Bartter's syndrome, Gitelman's syndrome or Liddle's syndrome), or other causes of metabolic alkalosis (milk-alkali syndrome, inadequate therapy by bicarbonate in metabolic acidosis). In patients with volume depletion, there is necessary to supplement volume deficiency by infusion therapy, usually by isotonic sodium chloride solution. The direct acidification is indicated in case of severe symptomatic alkalosis (pH >7.55, hydrogen carbonate serum level > 45 mmol/l). It is performed by means of ammonium chloride or arginine hydrochloride (especially if hypernatremia is present).

Mechanism of arginine action in case of hyperammonemia is its participation in ammonia metabolism. Arginine is a basic component of so called urea cycle that has a principal share on elimination of this highly toxic metabolite out of the organism. Ammonia is developed by oxidative deamination of amino acids (and other amines); in mitochondria, ammonia is fixed into so called carbamoyl phosphate that is conjugated with amino acid ornithine developing citrulline that is then in cytoplasm conjugated with aspartate through a few steps into arginine. Arginine is then hydrolyzed by means of arginase enzyme into urea and ornithine which is again returned into mitochondria and continues in the cycle.

With this mechanism also the action of arginine in hyperammonemia arising from hereditary urea cycle disorders is connected. 6 various enzymes are involved in the cycle. The individual enzyme deficiencies result in 6 types of urea cycle disorders (CPS1D, OTCD, ASSD, ASLD, ARG1D and NAGSD), all of which are treatable by means of arginine (with the exception of ARG1D type that is given by arginase deficiency and expressing particularly by hyperargininemia).

5.2. Pharmacokinetic properties

Arginine is a substance present naturally in the human body, which makes pharmacokinetic studies performing difficult.

Common physiological plasma levels of arginine are around 15 – 40 $\mu\text{mol/l}$. After a short-term infusion (30 min), arginine achieves maximum plasma concentration at the end of the infusion; such maximum concentrations range from 800 to 8 000 $\mu\text{mol/l}$ depending on the total administered dose (3-30 g). After finishing the infusion, plasma levels are dropping with $t_{1/2\alpha}$ of about 15 minutes; then a decrease in levels is slowed down with terminal half-time $t_{1/2\beta}$ of about 4 hours. Clearance slightly varies depending on the pharmacokinetic model used and the compartment. Clearance ranges from about 30 to about 70 litres/hour while volume of distribution is about 20 – 30 litres. Approximately 1/6 of the administered dose of arginine is eliminated by urine.

Arginine is metabolized intensively. Arginine is a part of a few metabolic cycles – urea cycle (ammonia detoxification and urea formation), citrate cycle (through 2-oxoglutarate) and citrulline cycle (NO formation). First, during arginine degradation, arginine is deaminated into ornithine. After

that, ornithine is changed via transamination into glutamic acid. Glutamic acid then enters Krebs cycle as 2-oxoglutarate.

Arginine intervenes with acid-base balance in cases of severe metabolic alkalosis. The product administration does not interfere in physiologic amino acids plasma levels on a long-term basis. Active substance goes through the placental barrier.

5.3. Preclinical safety data

Arginine is a natural substance of the body; no long-term trials with parenteral administration of arginine to laboratory animals have been performed. No clinically significant changes have been found out in peroral administration to sewer rats (in food up to 5 % for 13 weeks); only in some males from the highest dose group, temporary increased glucose blood levels were found out. NOEL in both males and females varied from 3 to 4 g/kg/day.

The preparation has been used in clinical praxis for series of years, and so far no case of carcinogenic or mutagenic effect has been found out.

6. PHARMACEUTIAL PARTICULARS

6.1. List of excipients

Aqua pro iniectio

6.2. Incompatibilities

No physical or chemical incompatibilities are known except of those solutions showing a different pH value.

6.3. Shelf life

2 years 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 preparation 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 as far as the opening/dilution was not performed under controlled and validated aseptic conditions.

6.4. Special precautions for storage

Do not freeze.

6.5. Nature and contents of container

Infusion glass bottle with a rubber stopper and a metallic closure, carton box.

Package size: 1x 80 ml, 1x 200 ml

20x 80 ml, 10x 200 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.

The product must not be used undiluted! The preparation is not intended for direct infusion. It is administered intravenously diluted with a higher amount of the carrying solution.

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

The preparation is intended only for single use!

All unused preparation or waste should be disposed according to the local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

76/921/95-C

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 22nd November 1995

Date of the last renewal of the authorisation: 20th September 2017

10. DATE OF REVISION OF THE TEXT

20th September 2017