sp.zn. sukls251288/2018

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ardeaosmosol Ma 10% infusion solution
Ardeaosmosol Ma 15% infusion solution
Ardeaosmosol Ma 20% infusion solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ardeaosmosol	**Ma 10%**	**Ma 15%**	**Ma 20%**
1000 ml of infusion solution contains:			
Mannitolum	100.0 g	150.0 g	200.0 g
Osmotic pressure	1 327 kPa	1 991 kPa	2 655 kPa
pH	4.0-7.0	4.0-7.0	4.0-7.0

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Infusion solution

Description of the preparation: clear, colourless or no more than slightly yellowish solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The promotion of diuresis within the prevention and treatment of the oliguric phase of acute renal failure caused by surgeries, shock, trauma, burns; supportive therapy in oedematous conditions (alternatively accompanied by ascites of nephrogenous, hepatic or cardiac origin).

The therapy and prevention of intracranial hypertension (traumatic, post-operative or caused by other underlying disease).

Forced diuresis to accelerate the elimination of toxic substances with renal clearance in the therapy of intoxications.

The treatment of intraocular hypertension (traumatic, post-operative, in narrow-angle glaucoma).

4.2. Posology and method of administration

The dosage is individual. It depends on the indication, the patient's health condition and on the therapeutic response.

Renal failure, oliguria: after the correction of plasma volume, the test dose of 0.2 g of mannitol/kg is administered within 3-10 minutes and the diuresis during next 1-2 hours is monitored. In case of the diuresis higher than 30 ml/hour or diuresis increased by 50 %, the administration of mannitol is continued via a slow intravenous infusion so that to maintain the diuresis higher than 40 ml/hour. A common dose for adults is 50-100 g/24 hours (0.7-1.4 g/kg/24 hours, 2.8 g/kg/24 hours maximum); a common dose in children is 0.25-2 g/kg/24 hours. In case of diuresis after the test dose lower than given above, the administration of mannitol solution is stopped.

Prophylaxis of acute renal failure: 0.3 g of mannitol/kg is administered 15-20 minutes before the surgery, 0.7 g/kg during the operation, 0.2-0.3 g/kg/hour after the surgery to maintain the diuresis. Electrolytes loss is replaced.

Cerebral oedema, intracranial or intraocular hypertension: 1.5-2 g/kg is given during 30-60 minutes or in the course of 24 hours divided into a few partial doses. To supplement electrolytes loss.
Oedematous conditions with hyponatremia: to be administered up to 1.5 g/kg/24 hours.

Forced diuresis: to achieve the diuresis of approximately 400 ml/hour, 1-2 g/kg during 1 hour is administered. In case of a good therapeutic response it is continued up to the dose of 1.5-2.9 g/kg/24 hours or the dose of 1-2 g/kg is repeated in 8 hours. Water and electrolytes loss should be monitored and replaced.

The product can be administered to adults or children without any age restriction

The dose of 105 g/24 hours can be exceeded only in case of diuresis higher than 100 ml/hour.

Method of administration:
Intravenous drop infusion in the closed system. The solution of 100 g/l can be administered via peripheral vein while the administration via central vein catheter is more advantageous. The solutions of 150 g/l or 200 g/l are to be administered only via central vein catheter.

4.3. Contraindications

Progressive renal failure with gradually increasing azotaemia, cardiac decompensation (particularly the left-sided one), severe dehydration, ionic imbalance, hyperosmolar condition, metabolic oedemas connected with a higher vascular permeability and fragility, intracranial bleeding except that in case of craniotomy, severe hypertension.

Anuria persistent even in case of sufficient hydration.

4.4. Special warnings and precautions for use

Serum osmolality, water and ion balance especially that of sodium and potassium is necessary to be monitored. It is impossible to evaluate specific urine gravity.

Mannitol is a hypertonic solution that may cause venous irritation when administered via peripheral vein and that is why a long-term infusion should be avoided.

When exposed to low temperatures, the solution may develop crystallisation. In that case warm the solution by immersing the closed pack into warm water and the crystals will be dissolved. Allow the solution to cool at room temperature and inspect whether crystals are not present. A short warming to 40 °C does not interfere the quality of the product.

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

Mannitol generates an increase in elimination of the drugs with renal clearance.

Mannitol augments the effect of other diuretics. It is not advisable to be administered together with furosemide.

When used concurrently with digoxin, the risk of digitalis toxicity is increased.

4.6. Fertility, pregnancy and lactation

The product has been used in the therapy for many decades. No adverse effects on the course of pregnancy or foetus/new-born health condition have been proved during the given period.

The use of the product during gravidity or lactation is not contraindicated.

4.7. Effects on ability to drive and use machines

The product of Ardeaosmosol Ma 10% (15%, 20%) is administered only in medical facilities and that is why the assessment of its impact on ability to drive or use machines is not relevant.

4.8. Undesirable effects

Ion imbalance with hyponatremia or hypokalemia as the most frequent events of imbalance, tissue dehydration, irritation of venous endothelium have been reported as potential undesirable effects with the product(s) of Ardeaosmosol Ma 10% (15%, 20%). Temporary hypervolemia or an increase in intracranial/intraocular pressure in case of a rapid emergency administration; those events are solved by a pharmacologic decrease in peripheral resistance for the exposed period.

Fever, acidosis, dryness of mouth, headache, nausea, vomiting, tachycardia or temporary muscle stiffness can occur.

Organ system class according to MedDRA database	Character of undesirable effect	Frequency of occurrence
Blood and lymphatic system disorders	Ion imbalance	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
	Tissue dehydration	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
	Hypervolemia, intracranial pressure increase	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
Cardiac disorders	Tachycardia	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
Vascular disorders	Irritation of venous endothelium	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
Gastrointestinal disorders	Nausea, vomiting	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.
General disorders and disorders non-classified somewhere else	Fever, headache, muscle stiffness	Accurate data are not available; it can be expected that they occur rarely with the frequency of occurrence >1/10,000 and < 1/1,000.

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 case of overdose, tissue dehydration and hyperosmolar condition is threatening; 5% glucose solution is administered. Hypervolemia is manageable by diuretics.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: infundabilium, ATC code: B05BC01 (Intravenous solutions – solutions producing osmotic diuresis - mannitol).

Mechanism of action – osmotically active solution for infusion

After intravenous administration, mannitol causes transfer of water from extravascular compartment into vascular bloodstream. After a rapid bolus administration, mannitol increases the circulating volume. Clinical impact of that is mild tissue dehydration, especially of the well perfused tissues, and then a spasmodic increase in diuresis. Mannitol is a non-metabolisable sugar. It is filterable at renal glomerulus and is not absorbed by renal tubules. Mannitol is pharmacologically inert.

5.2. Pharmacokinetic properties

a) general information – no active metabolites are generated

b) characterization of the active substance – it is a sugar alcohol, very easily water-soluble, fat-insoluble
   - Mannitol is minimally metabolized in the body, its main effect is the osmotic one.
   - Elimination half-life is approximately 100 minutes; onset of action after IV administration is in about 15 minutes.
   - Approximately 80 % from 100 g of mannitol administered appears in urine in 3 hours, a minor amount later.

c) Characterization after the administration in patients
   - It produces water transfer from erythrocytes, endothelium and from well-accessible extravascular compartment. It causes an increase of glomerular filtrate pressure and prevents water reabsorption in renal tubules. The diuretic effect causes an increase not only in water output but also in ion waste, particularly that of sodium and potassium.
   - It crosses the placenta, it does not cross the intact hemato-encephalic barrier.

5.3. Preclinical safety data

It is a product with a long-term usage ("well implemented therapeutic use") in which no preclinical studies had been performed with its introduction into the therapy.

There have been no undesirable effects known from the literature. The product used according to the recommended method is entirely safe.

6. PHARMACEUTIAL PARTICULARS

6.1. List of excipients

Aqua pro iniectione

6.2. Incompatibilities

With regard to the high mannitol concentration, particularly in 20% solution, it is not advisable to add any other medicines into the product!

It is not intended for administration via infusion set and one-source catheter together with plasma and blood products.

6.3. Shelf life

2 years provided that the package is intact.

The shelf life after the first opening:

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 as far as the opening was not performed under the controlled and validated aseptic conditions.

6.4. Special precautions for storage

Protect from frost.

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 100 ml, 1x 200 ml, 1x 500 ml
20x 80 ml, 20x 100 ml, 10x 200 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.

For intravenous administration.

The solution of Ma 10% can be administered via peripheral vein, solutions of Ma 15% and Ma 20% are to be administered only via central vein catheter.

When exposed to low temperatures, the solution may develop crystallisation. In that case warm the solution by immersing the closed pack into warm water and the crystals will be dissolved. Allow the solution to cool at room temperature and inspect whether crystals are not present. A short warming to 40 °C does not interfere the quality of the product.

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.

All unused product 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)

Ardeaosmosol Ma 10%: 76/917/95-A/C

Ardeaosmosol Ma 15%: 76/917/95-B/C

Ardeaosmosol Ma 20%: 76/917/95-C/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 authorization: 8th February 2017

10. DATE OF REVISION OF THE TEXT

17th July 2018