

Ditripentat-Heyl[®] (DTPA)



1. NAME OF THE MEDICINAL PRODUCT

Ditripentat-Heyl[®] (DTPA)

1 000 mg solution for injection

Active pharmaceutical ingredient: Calcium trisodium pentetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule with 5 ml injection solution contains

1 000 mg calcium trisodium pentetate (Ca-DTPA).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intravenous injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Long-term treatment for decorporation of transuranium heavy metal radionuclides (americium, plutonium, curium, californium, berkelium).

4.2 Posology and method of administration

Treatment of poisoning requires individual dosage, depending on the symptoms of intoxication.

Posology:

Adults: 1 ampoule per day

Initially 1 000 mg Ca-DTPA (about 15 mg/kg/d) in 20 ml physiological saline or 5 % glucose solution will be administered as a very slow i.v. injection (duration of the injection: about 15 min) or preferably as an infusion in 250 ml of the dilution solution over ½ to 2 h. The injection or infusion solution is to be used immediately after preparation.

Children and adolescents

Ditripentat-Heyl (DTPA) is not approved for the treatment of children and adolescents. In this case it can be switched to Zn-DTPA.

Method and duration of administration

The following dosage regimen is recommended for the therapy of adults:

- First week: 1 000 mg of Ca-DTPA on 5 days each
- Following 6 weeks: 1 000 mg of Ca-DTPA 2-3 times per week
- Following 6 weeks: therapy pause
- Further alternating 3 weeks therapy (1 000 mg of Ca-DTPA 2-3 times weekly) and 3 weeks therapy pause or alternatively 1 000 mg of Ca-DTPA i.v. every 2 weeks.
- The therapy pause can be also 4 to 6 months depending on the individual case.

At a long-term therapy zinc should be substituted regularly (e.g. 220 mg zinc sulfate daily). The long-term therapy can alternatively be switched to Zn-DTPA.

The necessary treatment can be very protracted (in individual cases about several years) and requires a multitude of injections.

The duration of the treatment depends on the clinical and laboratory results (radionuclide excretion in the urine). As long as the excretion rate of the metals is increased by the administration of DTPA, the therapy should be continued.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- during pregnancy,
- children and adolescents,
- hypercalcemia,
- patients with damages of the kidneys (nephrotic syndrome) or of the bone marrow (bone marrow depression, leucocytopenia, thrombocytopenia) or
- at oral uptake of radionuclides, as long as the nuclide is still in the gastrointestinal tract, since the complexed radionuclide may be better absorbed than the uncomplexed one.

Ditripentat-Heyl (DTPA) should not be used at incorporation with uranium, neptunium or cadmium.

4.4 Special warnings and precautions for use

Regular monitoring of the urine and blood status is indicated before and during treatment. The therapy with Ca-DTPA should be stopped at occurrence of changes of the kidneys (e.g. proteinuria, hematuria, urinary cast) or of the blood count. This also applies to occurrence of diarrhoea.

Monitoring of the urinary excretion of the radionuclide and of essential trace elements should be carried out regularly during long-term therapy.

Treatment of poisoning using Ca-DTPA does not exclude other measures for the treatment of poisoning, such as gastric lavage, dialysis, plasma exchange, surgical removal of the depot, etc.

The daily dose should not be divided into several smaller doses.

The blood pressure should be monitored regularly during the administration of Ditripentat-Heyl (DTPA).

4.5 Interaction with other medicinal products and other forms of interaction

At simultaneous administration of Ditripentat-Heyl (DTPA) with essential heavy metals, such as zinc or iron, the drugs can mutually cancel each other out in their effectiveness. Therefore it is recommended to carry out a possible necessary substitution of the trace elements temporally staggered.

4.6 Fertility, pregnancy and lactation

Ditripentat-Heyl (DTPA) may not be used during pregnancy. In this case it can be switched to Zn-DTPA.

Women exposed to radionuclides should not breastfeed in general.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following frequency details are used as a base for the assessment of the side effects:

Very common: ($\geq 1/10$)

Common: ($\geq 1/100$ to $< 1/10$)

Uncommon: ($\geq 1/1\ 000$ to $< 1/100$)

Rare: ($\geq 1/10\ 000$ to $< 1/1\ 000$)

Very rare: ($< 1/10\ 000$)

Unknown: Frequency cannot be estimated from the available data

Depending on the type and severity of the intoxication, the correspondingly required dosage and the duration of treatment the following undesirable effects may occur with individually differing frequencies.

Immune system disorders

Rare: Allergic reactions which can result in skin reactions.

Metabolism and nutrition disorders

DTPA increases the excretions of some trace elements, particularly of zinc. In individual cases with long-term treatment clinically manifest zinc deficiency was described (alopecia, skin reactions, mucosa changes [exanthemas, enanthemas]). The symptoms were reversible after the supplementation of zinc. A reversible ageusia was described for one patient.

The increased zinc excretion is presumably also the main cause for other side effects. Kidney lesions, intestine disturbances and bone marrow damages (thrombocytopenia) were reported.

Nervous system disorders

Rare: Paresthesias

Cardiac disorders

Rare: Reduction of blood pressure

Vascular disorders

Local symptoms of irritation (thrombophlebotic reactions) have been reported on rapid i.v. injection.

Skin and subcutaneous tissue disorders

Rare: Rhinitis vasomotorica, allergic skin reactions

Renal and urinary disorders

DTPA can lead to kidney damages (nephrotic syndrome and renal insufficiency). A deterioration of the kidney function has been proved at prelesion of the kidney. A special caution is therefore advised at poisonings with metals which have kidney damaging effects themselves. The changes at the kidneys are reversible after removing DTPA.

Injury, poisoning and procedural complications

When Ca-DTPA is administered repeatedly with too short regeneration intervals between the individual administrations, the following may occur: delayed fever reaction, nausea, vomiting, diarrhoea, shivering, headaches, pruritus and muscular cramps.

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 Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Symptoms of overdose

High doses of Ca-DTPA can lead to severe damages of the kidneys, of the intestinal mucosa and of the liver. As a cause a depletion of zinc and manganese is suspected.

Therapy of overdose

At appearance of corresponding symptoms the trace elements have to be checked and to be substituted. In addition, a symptomatic therapy can be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote for decorporation of transuranic heavy metal radionuclides.

ATC-Code: V03AB47 Pentetic acid

Ca-DTPA is the calcium sodium salt of the pentetic acid. It is a complexing agent from the group of synthetic polyaminopolycarboxylic acids which have a high affinity for many heavy metals and radionuclides and forms stable, water soluble complexes (= chelates) with them. The calcium ion is exchanged for the corresponding metal ion, if it has a greater binding constant to DTPA. As these metal chelates are better excreted than the metal itself, Ca-DTPA promotes the elimination of the metals present primarily in the extracellular space. Excretion takes place predominantly via the kidneys with the urine.

As chelating agent Ca-DTPA can result in imbalances of mineral metabolism, especially of zinc and manganese. So metalloenzymes like δ -aminolaevulinic acid dehydratase (ALAD) can be inhibited temporarily. Concurrent oral administration of zinc or change to Zn-DTPA for long-term treatment may lead to sufficient zinc levels and avoid adverse drug reactions.

5.2 Pharmacokinetic properties

After oral administration the enteral absorption of DTPA is less than 10 %. When administered as an aerosol via the lungs about 20 - 30 % of the inhaled dose is absorbed. After intraperitoneal or intramuscular administration DTPA is rapidly and completely absorbed.

The distribution volume corresponds to the extracellular water. Only a small amount is bound to plasma proteins. DTPA is unable to penetrate cell membranes to any great degree. There is no enrichment in any specific organs.

DTPA is practically not metabolised. It is rapidly and almost completely eliminated renally by glomerular filtration. The excretion in the faeces is < 3 %. The plasma half-life is about 20 - 60 minutes. Only a small fraction that is bound to the plasma proteins has a half-life of > 20 h.

5.3 Preclinical safety data

a) Acute toxicity

The acute LD₅₀ of Ca-DTPA is 6.2 g/kg (mouse i.p.), whereas the animals died within 48 hours. In rats the LD₅₀ is 3.5 g/kg (i.p.).

b) Chronic toxicity

Long-term studies with low doses of Ca-DTPA did not lead to side effects in mice. High doses resulted in nephrotic renal disorders, which are reversible after discontinuing Ca-DTPA. Furthermore, disorders of the gastrointestinal epithelium were observed. Other organs did not show distinct histopathological changes. A single high dosed administration will be better tolerated than a repeated administration in lower amounts.

c) Mutagenicity / cancerogenicity

There are no investigations on mutagenicity and cancerogenicity available.

d) Reproductive toxicity

In mice high doses of Ca-DTPA lead to fetal mortality and increased rates of congenital abnormalities especially in the first or second trimester of pregnancy. The NOEL for teratogenic effects is <358 mg/kg s.c. in mice. As a cause an influence on the zinc and manganese levels and their effect on the activity specific metalloenzymes is discussed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate, sodium hydroxide, pentetic acid, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. In particular, the simultaneous administration of essential minerals like zinc or manganese and Ditripentat-Heyl (DTPA) should be avoided.

6.3 Shelf life

The shelf-life is 5 years.

The drug product should not be used after the expiry date given on the label and on the package.

The injection or infusion solution is to be used after the preparation immediately.

6.4 Special precautions for storage

Do not store above 25 °C.

Keep in the original packing.

Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

5 ampoules each containing 5 ml of injection solution

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

6813281.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2005

Date of latest renewal: 21.04.2005

10. DATE OF REVISION OF THE TEXT

February 2015

11. GENERAL CLASSIFICATION FOR SUPPLY

For sale in pharmacies only