

**Zink-Trinatrium-pentetat
(Zn-DTPA)**



1. NAME OF THE MEDICINAL PRODUCT

Zink-Trinatrium-pentetat (Zn-DTPA)
1055 mg / 5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule with 5 ml solution for injection contains:
1 055 mg of trisodium zinc pentetate (Zn-DTPA)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to slightly yellowish solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The dosage of Zink-Trinatrium-pentetat (Zn-DTPA) is adjusted according to type and severity of intoxication.

The following are average doses:

Adults: 1 ampoule per day
Children: 25 - 50 mg per kg body weight and day

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

- First week: 1 055 mg of Zn-DTPA daily on 5 days of the week
- Weeks 2 to 7: 1 055 mg of Zn-DTPA 2-3 times a week
- Weeks 8 to 13: therapy-free period
- Followed by: 3-week treatment (1 055 mg of Zn-DTPA 2-3 times a week) and subsequent 3-week therapy-free period or alternatively: 1 055 mg of Zn-DTPA once every 2 weeks
- Depending on the individual case, the therapy-free period may also be 4 to 6 months.

Method of administration

Intravenous use

The daily dose will be administered dissolved in 20 ml of physiological saline solution or in 5 % glucose solution as a very slow i.v. injection (duration of the injection: about 15 minutes) or preferably as an infusion in 250 ml of the dilution solution over ½ to 2 h.

The duration of treatment depends on the clinical and laboratory findings (heavy metal excretion in the urine). The treatment should be continued for as long as the excretion rate of the metals is increased by the administration of DTPA.

The necessary treatment can be very protracted (in individual cases for several years) and may require numerous infusions.

During the use care should be taken to ensure adequate hydration.

4.3 Contraindications

- hypersensitivity to the active substance, its salts or to any of the excipients listed in section 6.1
- hyperzincaemia,
- 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 non-complexed one.

Zn-DTPA should not be used for incorporation with uranium, neptunium or cadmium.

4.4 Special warnings and precautions for use

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

Regular monitoring of the urine and blood status is indicated before and during treatment.

The blood pressure should be monitored regularly during the administration of Zink-Trinatrium-pentetat (Zn-DTPA).

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

For acute poisoning, initiation of treatment with the more potent trisodium calcium pentetate is recommended. Long-term treatment should be continued with the less toxic Zink-Trinatrium-pentetat (Zn-DTPA) then.

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

One ampoule contains 6.06 mmol (139.5 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions are known.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available on the effect of Zink-Trinatrium-pentetat on male and female fertility.

Pregnancy

There is insufficient experience about the safety of Zink-Trinatrium-pentetat (Zn-DTPA) in humans when used during pregnancy. Animal studies have not shown embryotoxic/teratogenic effects.

In case of pregnancy, the risk of poisoning versus the risk of drug treatment should be carefully evaluated. If the use of Zink-Trinatrium-pentetat (Zn-DTPA) during pregnancy is necessary for a vital indication, then the mineral balance should be monitored in order to provide the child with essential trace elements.

Lactation

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 corresponding required dosages 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.

Cardiac disorders

Rare: reduction of the blood pressure

Vascular disorders

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

Skin and subcutaneous tissue disorders

Rare: allergic reactions in the form of skin reactions

Injury, poisoning and procedural complications

When Zn-DTPA is administered repeatedly with too short regeneration intervals between the individual administrations, the following may occur: nausea, vomiting, diarrhoea, fever, 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

At present, there are no known symptoms of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote for radionuclide intoxication
ATC-Code: V03AB47 Pentetic acid

Zink-Trinatrium-pentetat (Zn-DTPA)



Mechanism of action

Zn-DTPA is the zinc 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 form stable, water soluble complexes (= chelates) with them. During this reaction the zinc 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, Zn-DTPA promotes the elimination of the metals present primarily in the extracellular space. Excretion takes place predominantly via the kidneys with the urine.

5.2 Pharmacokinetic properties

Absorption

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 absorbed rapidly and completely.

Distribution

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.

Elimination

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

Acute toxicity

The toxicity of Zn-DTPA is low. This applies both to the lethality and to the histopathological changes in the kidneys, small intestine or bones. However, Ca-DTPA in high dosage can induce degenerative damage of the renal tubules and the intestinal mucosa.

The acute LD₅₀ for Zn-DTPA is about 30x higher than that of Ca-DTPA. In the adult mouse it is > 10 g/kg.

Chronic toxicity

Long-term investigations with a low dose did not show any side-effects in mice.

Mutagenicity / cancerogenicity

There are no investigations on mutagenicity and cancerogenicity available.

Reproductive toxicity

Zn-DTPA did not lead to any teratogenic effects in mice and rats even at doses that were several times the therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, pentetic acid, water for injections, zinc oxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Zink-Trinatrium-pentetat (Zn-DTPA)



6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

5 ampoules each containing 5 ml of solution for injection

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Heyl Chem.-pharm. Fabrik GmbH & Co. KG
Kurfürstendamm 178-179
10707 Berlin
Germany

Phone: + 49 30 81696-0
Fax: + 49 30 81696-33
E-mail: info@hey1-berlin.de
Website: www.hey1-berlin.de

8. MARKETING AUTHORISATION NUMBER

6813967.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2003
Date of latest renewal: 24 November 2003

10. DATE OF REVISION OF THE TEXT

April 2018

11. GENERAL CLASSIFICATION FOR SUPPLY

By prescription only