Zn-DTPA is supplied as a clear, colorless, hyperosmolar (1260 mOsmol/kg) solution in a colorless ampoule containing 5 mL. The ampoule contents are sterile, non-pyrogenic and suitable for intravenous administration. Each mL of solution contains the equivalent of 200 mg pentetate zinc trisodium (obtained from 150.51 mg pentetic acid, 31.14 mg zinc oxide and NaOH) and water for injection, USP. The pH of the solution is adjusted with NaOH and is between 6.5 – 7.5.

**CLINICAL PHARMACOLOGY**

**General**

Zn-DTPA forms stable chelates with metal ions by exchanging zinc for a metal of greater binding capacity. The chelating agent is then excreted by glomerular filtration into the urine. In animal studies, Zn-DTPA forms less stable chelates with uranium and neptunium in vivo resulting in deposition of these elements in tissues including the bone. Zn-DTPA treatments are not expected to be effective for uranium and neptunium. Radiopaque iodine is not bound by Zn-DTPA.

**Pharmacodynamics**

In a study of rodents internally contaminated with plutonium, the rate of plutonium elimination was measured following intravenous administration of Ca-DTPA and Zn-DTPA as a single dose of 10 to 1,000 µg/kg (0.54 – 54 x a maximum human dose, MHD). When treated within one hour of internal contamination, Ca-DTPA resulted in a 10-15 fold higher rate of elimination of plutonium in the urine as compared to Zn-DTPA. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after internal contamination when the radionuclide is still circulating and readily available for chelation. After the first dose of Ca-DTPA, maintenance treatment with either Ca-DTPA or Zn-DTPA resulted in similar rates of elimination of radioactivity. However, at comparable doses, Zn-DTPA had less toxicity (e.g., less depletion of trace metals, lower rate of mortality, the absence of kidney and liver vacuolization, and absence of small bowel hemorrhagic lesions).

In another study, rodents contaminated with aerosolized plutonium and americium were treated with Ca-DTPA and Zn-DTPA. The treatment schedule involved inhalation of Ca-DTPA 2 µmol/kg (0.11 MHD) 30 minutes after contamination followed by inhalation of Zn-DTPA 2 µmol/kg at approximately 6 hours, 1, 2, 3, and 6 days, then twice weekly to day 20 or day 27. The treatment regime reduced the lung deposit of plutonium and americium to 1-2% of that in untreated animals. Systemic deposit in liver and skeleton were reduced by half.

**Distribution**

Following intravenous administration, Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of Zn-DTPA penetrates into erythrocytes or other cells. No accumulation of Zn-DTPA is specific organs has been observed. There is little or no binding of the chelating agent by the renal parenchyma.

**Metabolism**

Zn-DTPA undergoes a minimal amount of metabolic change in the body.

**Adverse Metabolic Effects:** Zn-DTPA results in minimal depletion of magnesium and manganese.
Two individuals experienced cough and/or wheezing with nebulized Ca-DTPA therapy however there was no report of such events with nebulized Zn-DTPA.

OVERDOSAGE
Dose of nebulized Zn-DTPA has not been reported.

DOSE AND ADMINISTRATION
Chelation treatment is most effective if administered within the first 24 hours after internal contamination and should be started as soon as possible after suspected or known internal contamination. However, even when treatment cannot be started right away, individuals should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination, however the chelating effects of Zn-DTPA are greatest when the radiocontaminants are still circulating or are in intestinal fluids. The effectiveness of chelation decreases with time following internal contamination as the radiocontaminants become sequestered in liver and bone.

Individuals should drink plenty of fluids and void frequently to promote dilation of the radioactive chelate in the urine and minimize radiation exposure directly to the bladder. If internal contamination with radiocontaminants other than plutonium, americium, or curium, or unknown radiocontaminants is suspected, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

Initial Dose
IT IS PREFERABLE TO ADMINISTER CA-DTPA, IF AVAILABLE, AS THE INITIAL DOSE DURING THE FIRST 24 HOURS AFTER INTERNAL CONTAMINATION BECAUSE CA-DTPA IS MORE EFFECTIVE THAN ZN-DTPA DURING THIS TIME PERIOD. AFTER 24 HOURS, ZN-DTPA AND CA-DTPA ARE EQUALLY EFFECTIVE.

Adults and Adolescents: A single 1.0 gram initial dose of Zn-DTPA administered intravenously.

Pregnancy (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously not to exceed 1.0 gram.

Renally impaired patients: No dose adjustment is needed. However, renal impairment may reduce the rate at which chelators remove radiocontaminants from the body. In heavily contaminated patients with renal impairment, dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public.

Maintenance Treatment
Adults and Adolescents: The recommended maintenance dose of Zn-DTPA is 1.0 gram once a day administered intravenously.

Pregnancy (less than 12 years of age): The recommended maintenance dose of Zn-DTPA is 14 mg/kg once a day administered intravenously. The maximum daily dose should not exceed 1.0 gram per day.

Renally impaired patients: No dose adjustment is needed. The duration of chelation treatment depends on the amount of internal contamination and individual response to treatment. (See Monitoring)

Methods of Administration
The intravenous route is recommended and should be used if the route of internal contamination is not known or if multiple routes of internal contamination are likely. Zn-DTPA solution (1 gram in 5 mL) should be administered either with a slow intravenous push over a period of 3-4 minutes or by intravenous infusion over 30 minutes diluted in 100-250 mL of 5% dextrose in water (D5W), Ringers Lactate, or Normal Saline.

In individuals whose internal contamination is only by inhalation, Zn-DTPA can be administered by nebulized inhalation as an alternative route of administration. Zn-DTPA should be diluted for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, individuals should be encouraged to avoid swallowing any expectorated material. Some individuals may experience respiratory adverse events after inhalation therapy. (See WARNINGS) The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population. The safety and effectiveness of the intramuscular route of injection have not been established.

Handling
OPC ampoule: to open, turn so that the point faces upward and break off the neck with a downward movement.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The product may be filtered using a sterile filter if solution and container permit. The product may be filtered using a sterile filter if solution and container permit. The product may be filtered using a sterile filter if solution and container permit. The product may be filtered using a sterile filter if solution and container permit. The product may be filtered using a sterile filter if solution and container permit.

Monitoring
Whichever, obtain baseline blood and urine samples (CBC with differential, BUN, serum chemistries and electrolytes, urinalysis and blood and urine radioassays) before initiating treatment.

To establish an elimination curve, a quantitative baseline estimate of the total internalized transuranium element(s) and measures of elimination of radioactivity should be obtained by appropriate whole-body counting, by bioassay (e.g., biodosimetry), or fecal/urine sample whenever possible.

During Treatment:
• Measure the radioactivity in blood, urine, and fecal samples weekly to monitor the radioactive contaminant elimination rate.
• Monitor CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis measurements regularly.
• Record any adverse events from Zn-DTPA.

HOW SUPPLIED
Zn-DTPA is supplied as a sterile solution in 5 mL single-use clear glass ampoules at a concentration of 200 mg/mL for intravenous use. Each ampoule contains the equivalent of 1000 mg of pentetate zinc trisodium.

NDC 52919-002-003, 5 mL single-use ampoules, package of 10.

Storage
Store between 15 - 30°C (59 - 86°F).

COLLECTION OF PATIENT TREATMENT DATA
To develop long-term response data and information on the risk of developing late malignancy, detailed information on patient treatment should be provided to the manufacturer (see attached Pad of Patient Treatment Data Forms. In the case you need additional forms, please see the following website: www.hameln-pharmaceuticals.com). These data should include a record of the radioactive body burden and bioassay results at defined time intervals, a description of measurement methods to facilitate analysis of data, and adverse events. Questions regarding the use of Zn-DTPA for the treatment of internal contamination with transuranium elements may be referred to:
hameln Pharmaceuticals GmbH
Langes Feld 13
31789 Hameln, Germany
Tel.: +49-5151-581-0
Fax.: +49-5151-581-258
e-mail: welcome@hm-ph.com

contact person: Dr. Mathias Dewald
Tel.: +49-5151-581-214
Fax.: +49-5151-581-581
e-mail: m.dewald@hm-ph.com

Zn-DTPA Patient treatment Data
Send to:
hameln Pharmaceuticals GmbH
Langes Feld 13, 31789 Hameln, Germany

Date of report:

Unique patient identifier

Patient ID
Name:
Date of birth:
Sex: Male Female
Address:
Phone:
Hospitalization: No Yes Where?

Criteria for Diagnosis
Date/time of exposure:
Geographic location/details of exposure:
Lab/field confirmed exposure; method:

Symptoms of Acute Radiation Syndrome:

Contamination
Transuranium element(s) confirmed suspected,
list element(s):
Route (check all that apply): Skin Inhalation Wound Burn Ingestion
Anatomic area affected:
Initial radioactivity measurement:
How measured:

Decontamination
External: Skin washed with: Wound excised/washed:
Contraindications to aerosolized treatment
(Iso lung disease, cough, dyspnea, chest tightness, wheezing)?

Internal:
Zn-DTPA Date/time of initial dose:
Amount:
Total doses:
Route:

Adverse Reaction to Treatment
Adverse Reaction(s) to treatment?
No Yes; provide details:
Vital signs: Baseline Stable Unstable:
Subsequent (if abnormal):
Disposition of patient/outcome of treatment:

Treatment Team Data
Report completed by:
Title:
Organization/affiliation:
Phone:
Email:

Comments

Attach Copy of Emergency Records to this Form

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