

PENTETATE CALCIUM TRISODIUM- pentetate calcium trisodium injection, solution, concentrate
hameln pharma plus gmbh

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PENTETATE CALCIUM TRISODIUM INJECTION safely and effectively.

See full prescribing information for PENTETATE CALCIUM TRISODIUM INJECTION.

Pentetate calcium trisodium injection (Ca-DTPA)

For intravenous or inhalation administration

Initial U.S. Approval: 2004

WARNING: ASTHMA EXACERBATION WITH NEBULIZATION and DEPLETION OF TRACE METALS DURING THERAPY

See full prescribing information for complete boxed warning.

- Nebulized Ca-DTPA may be associated with asthma exacerbation. (5.1)
- Ca-DTPA is associated with depletion of trace metals such as zinc. The magnitude of depletion increases with split daily dosing, with increasing dose and with increased treatment duration. Only a single dose of Ca-DTPA is recommended. Use Zn-DTPA if additional chelation therapy is indicated. Monitor serum zinc levels, serum creatinine, BUN, electrolytes, urinalysis and blood cell counts during Ca-DTPA or Zn-DTPA therapy. (2.4, 5.2)

----- **INDICATIONS AND USAGE** -----

Pentetate calcium trisodium injection is a radiomitigation chelator indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. (1)

----- **DOSE AND ADMINISTRATION** -----

Chelation treatment is most effective if administered within the first 24 hours. (2.1, 2.2)

In adults and adolescents, administer intravenously a single 1.0 gram Ca-DTPA dose. (2.1)

In children less than 12 years of age, administer intravenously, a single 14 mg/kg Ca-DTPA dose, not to exceed 1.0 gram. (2.1)

Zn-DTPA is recommended for maintenance chelation therapy after the first 24 hours. If Zn-DTPA is unavailable, chelation therapy may continue with Ca-DTPA. (2.1)

See Full Prescribing Information for dose (2.1) and nebulized chelation therapy (2.3)

----- **DOSE FORMS AND STRENGTHS** -----

1000 mg / 5 mL single-use ampoules (3)

----- **CONTRAINDICATIONS** -----

None (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Nebulized Ca-DTPA may be associated with exacerbation of asthma. Monitor patients for signs and symptoms of asthma exacerbation when administering Ca-DTPA by the inhalation route. (5.1)
- Ca-DTPA is associated with depletion of endogenous trace metals (e.g., zinc, magnesium, manganese). (5.2)
- Take appropriate safety measures to minimize contamination of care-takers by contaminated body fluids. (5.3)
- Use Ca-DTPA with caution in individuals with severe hemochromatosis. (5.4)

----- **ADVERSE REACTIONS** -----

There is limited experience with Ca-DTPA. Adverse events included headache, lightheadedness, chest pain, allergic reaction, dermatitis, metallic taste, nausea and diarrhea, and injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact the hameln Pharmacovigilance Department at +44 (0) 7706 210 133 or drugsafety@hameln.co.uk or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. (7)

----- **USE IN SPECIFIC POPULATIONS** -----

- **Pregnancy:** Based on animal data, Ca-DTPA may cause fetal harm. Chelation treatment of pregnant women should begin and continue with Zn-DTPA. If Zn-DTPA is not available, Ca-DTPA should be used. (8.1)
- **Nursing Mothers:** Women with known or suspected internal contamination with radiocontaminants should not breast

- feed, whether or not they are receiving chelation therapy. (5.3, 8.3)
- Pediatric Use: Safety and effectiveness of intravenous Ca-DTPA were extrapolated from adults. Safety and effectiveness of the nebulized route of administration have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ASTHMA EXACERBATION WITH NEBULIZATION and DEPLETION OF TRACE METALS DURING THERAPY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dose

2.2 General

2.3 Methods of Administration

2.4 Monitoring

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Asthma Exacerbation

5.2 Depletion of Body Trace Mineral Stores

5.3 Risks to Care-takers

5.4 Risks for Patients with Hemochromatosis

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing mothers

8.4 Pediatric use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.2 Storage

16.3 Handling

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA EXACERBATION WITH NEBULIZATION and DEPLETION OF TRACE METALS DURING THERAPY

- Nebulized Ca-DTPA may be associated with asthma exacerbation. (5.1)
- Ca-DTPA is associated with depletion of trace metals such as zinc. The magnitude of depletion increases with split daily dosing, with increasing dose and with increased treatment duration. Only a single dose of Ca-DTPA is recommended. Use Zn-DTPA if additional chelation therapy is indicated. Monitor serum zinc levels, serum creatinine, BUN, electrolytes, urinalysis and blood cell counts during Ca-DTPA or Zn-DTPA therapy. (2.4, 5.2)

1 INDICATIONS AND USAGE

Ca-DTPA is indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

2 DOSAGE AND ADMINISTRATION

2.1 Dose

Administer Ca-DTPA as the initial dose during the first 24 hours after internal contamination. Ca-DTPA is more effective than Zn-DTPA during this time period. If Ca-DTPA is not available, use Zn-DTPA as the initial therapy. On the next day, if additional chelation therapy is indicated, begin daily treatment with Zn-DTPA (see Zn-DTPA labeling). If Zn-DTPA is not available, chelation therapy may continue with Ca-DTPA; concomitant mineral supplements containing zinc should be given. [See Warnings and Precautions (5.2)]

Do not administer more than one dose per 24 hour period.

Adults and Adolescents

A single 1.0 gram initial dose of Ca-DTPA administered intravenously.

Children less than 12 years of age

A single 14 mg/kg initial dose of Ca-DTPA administered intravenously, not to exceed 1.0 gram.

If Zn-DTPA is not available

For adults and adolescents, the recommended maintenance dose is 1.0 gram Ca-DTPA once daily administered intravenously. For children less than 12 years of age, the recommended maintenance dose is 14 mg/kg Ca-DTPA once daily administered intravenously, not to exceed 1.0 gram per day.

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.

2.2 General

Chelation treatment is most effective if administered within the first 24 hours after internal contamination. Start chelation treatment as soon as possible after suspected or known internal contamination. When treatment cannot be started right away, give chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination. The chelating effects of Ca-DTPA are greatest when radiocontaminants are still circulating or are in interstitial fluids. The effectiveness of chelation decreases with time following

internal contamination as the radiocontaminants become sequestered in liver and bone.

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).

2.3 Methods of Administration

Use intravenous administration of Ca-DTPA if the route of internal contamination is not known or if multiple routes of internal contamination are likely. Administer Ca-DTPA solution (1 gram in 5 mL) either with a slow intravenous push over a period of 3-4 minutes or by intravenous infusion 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 within the preceding 24 hours, Ca-DTPA can be administered by nebulized inhalation as an alternative route of administration. Dilute Ca-DTPA for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, encourage patients to avoid swallowing any expectorant. Some individuals may experience respiratory adverse events after inhalation therapy. *[See Warnings and Precautions (5.1)]*

The safety and effectiveness of the nebulized route of administration have not been established in the pediatric population.

The safety and effectiveness of the intramuscular route of injection have not been established. *[See Overdosage (10)]*

2.4 Monitoring

When possible, obtain baseline blood and urine samples (CBC with differential, serum creatinine, BUN and electrolytes, urinalysis, and blood and urine radioassays) before initiating treatment.

Ca-DTPA must be given with very careful monitoring of serum zinc and complete blood counts. When appropriate, administer vitamin or mineral supplements that contain zinc. *[See Warnings and Precautions (5.2)]*

To establish an elimination curve, obtain a quantitative baseline estimate of the total internalized transuranium element(s) and measures of elimination of radioactivity 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 creatinine and electrolytes, and urinalysis. If the individual is receiving more than one dose of Ca-DTPA, consider mineral supplementation as appropriate based on these laboratory tests.
- Record any adverse events from Ca-DTPA.

3 DOSAGE FORMS AND STRENGTHS

1000 mg / 5 mL single-use ampoules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma Exacerbation

Nebulized Ca-DTPA is associated with asthma exacerbation. Monitor patients for signs and symptoms of asthma exacerbation when administering Ca-DTPA by the inhalation route. [See *Adverse Reactions (6)*]

5.2 Depletion of Body Trace Mineral Stores

Ca-DTPA is associated with depletion of endogenous trace metals (e.g., zinc, magnesium, manganese). The magnitude of depletion increases with split daily dosing, with increasing dose, and with increased treatment duration. [See *Clinical Pharmacology (12.3)*] Only a single initial dose of Ca-DTPA is recommended. Use Zn-DTPA if additional chelation therapy is indicated (See Zn-DTPA labeling). If Zn-DTPA is not available, chelation therapy may continue with Ca-DTPA but give mineral supplements containing zinc concomitantly, as appropriate.

Monitor serum zinc levels, electrolytes and blood cell counts during Ca-DTPA or Zn-DTPA therapy. Give mineral or vitamin plus mineral supplements that contain zinc as appropriate. [See *Dosage and Administration (2.4)*]

5.3 Risks to Care-takers

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with plutonium, americium, or curium, Ca-DTPA treatment increases excretion of radioactivity in the urine. Take appropriate safety measures to minimize contamination of others. [See *Patient Counseling Information (17)*]

5.4 Risks for Patients with Hemochromatosis

Use of only a single Ca-DTPA dose is particularly important for patients with hemochromatosis. Deaths have been reported in patients with severe hemochromatosis who received Ca-DTPA for more than 1 day, by intramuscular injection. [See *Overdosage (10)*]

6 ADVERSE REACTIONS

In the U.S. Registry, a total of 646 individuals received at least one dose of either Ca-DTPA or Zn-DTPA. Of these, 632 received Ca-DTPA by one or more routes of administration. Three hundred and twenty-six individuals were dosed by inhalation, 293 by intravenous injection, and 60 by other or unknown routes of administration.

Of the individuals that received Ca-DTPA, 393/632 (62%) received one dose and 65 (10%) received two doses. The remaining 174 individuals received three or more doses. The largest number of Ca-DTPA doses to a single individual was 338 delivered over 6.5 years. Overall, the presence or absence of adverse events was recorded in 310/646 individuals. Of these 19 (6.1%) individuals reported at least one adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 18 adverse events occurred after treatment with Ca-DTPA. Adverse events included headache, lightheadedness, chest pain, allergic reaction, dermatitis, metallic taste, nausea and diarrhea, and injection site reactions.

Cough and/or wheezing were experienced by 2 individuals receiving nebulized Ca-DTPA, one of whom had a history of asthma.

In literature reports, prolonged treatment with Ca-DTPA resulted in depletion of zinc, magnesium, manganese and possibly metalloproteinases. [See *Warnings and Precautions (5.2)*]

7 DRUG INTERACTIONS

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. When an individual is contaminated with multiple radiocontaminants, or when the radiocontaminants are unknown, additional therapies may be needed (e.g., Prussian blue, potassium

iodide).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of Ca-DTPA use in pregnant women. Ca-DTPA chelation therapy causes depletion of body stores of zinc, a trace metal essential for fetal development [see *Warnings and Precautions (5.2)*]. The consequences of zinc depletion and results of animal studies suggest a teratogenic risk in humans. Ca-DTPA was teratogenic and embryotoxic in mice at daily doses 2 to 8 times the recommended daily human dose, based on body surface area (BSA), with a dose-dependent increase in the frequency of gross malformations. Ca-DTPA was teratogenic in dogs at approximately half the recommended daily human dose based on BSA, as described below. There are no animal or human data evaluating the teratogenic effect of a single dose of Ca-DTPA. Ca-DTPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Chelation treatment of pregnant women should begin and continue with Zn-DTPA, if available, except in cases of high internal radioactive contamination. Because Ca-DTPA is more effective than Zn-DTPA in the first 24 hours after internal contamination, it may be appropriate to use a single dose of Ca-DTPA with vitamin or mineral supplements that contain zinc as the initial treatment.

Animal Data

Ca-DTPA is teratogenic and embryotoxic in mice during any period of gestation following five daily subcutaneous injections of 720 to 2880 micromol Ca-DTPA/kg [2 to 8 times the recommended daily human dose of 1 gram based on BSA]. The frequency of gross malformations (e.g., exencephaly, spina bifida, cleft palate, ablepharia, and polydactyly) and fetal mortality increased with dose, with higher susceptibility in early and mid gestation. Five daily doses of 360 micromol Ca-DTPA/kg in mice, approximately equivalent to the recommended daily human dose (based on BSA) produced no harmful effects. A study of two pregnant dogs given daily intravenous injections of 30 micromol Ca-DTPA/kg (approximately half the recommended daily human dose based on BSA) from implantation until parturition showed severe teratogenic effects (brain damage), and decrease in the number of surviving pups.

8.3 Nursing mothers

It is not known whether Ca-DTPA is excreted in human milk. Radiocontaminants are known to be excreted in breast milk. Women with known or suspected internal contamination with radiocontaminants should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. [See *Warnings and Precautions (5.3)*]

8.4 Pediatric use

The safety and effectiveness of Ca-DTPA were established in the adult population and efficacy was extrapolated to the pediatric population for the intravenous route based on the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an intravenous drug that is renally cleared [See *Dosage and Administration (2.1)*]. The safety and effectiveness of the nebulized route of administration have not been established in the pediatric population.

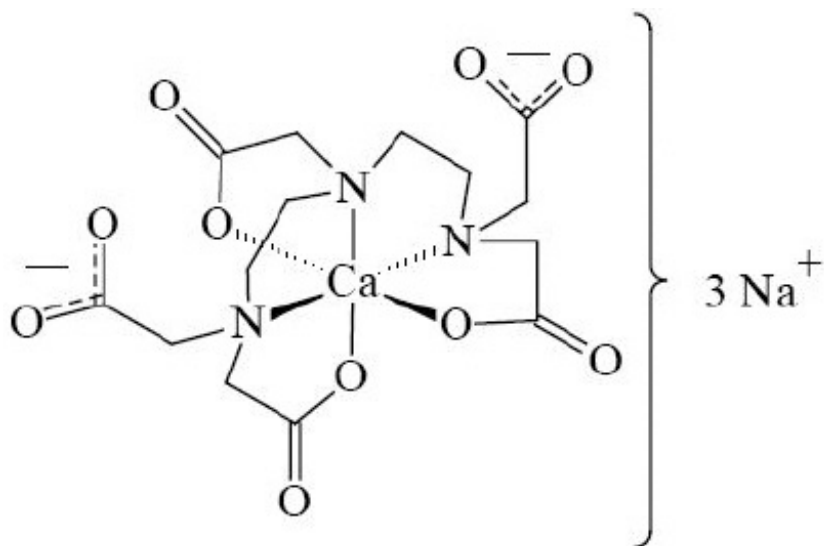
10 OVERDOSAGE

In previous clinical studies, three deaths were reported in patients with severe hemochromatosis who

were treated with daily intramuscular Ca-DTPA dosed up to 4 gram per day to reduce iron stores. One patient became comatose and died after receiving a total of 14 grams Ca-DTPA, and the other two died after two weeks of daily treatment. Causal association with these events and the drug has not been established. [See Warnings and Precautions (5.4)]

11 DESCRIPTION

Pentetate calcium trisodium injection contains the sodium salt of calcium diethylenetriaminepentaacetate. Pentetate calcium trisodium is also known as trisodium calcium diethylenetriaminepentaacetate and is commonly referred to as Ca-DTPA. It has a molecular formula of $\text{Na}_3\text{CaC}_{14}\text{H}_{18}\text{N}_3\text{O}_{10}$ and a molecular weight of 497.4 Daltons. It is represented by the following structural formula:



Ca-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 calcium trisodium (obtained from 158.17 mg pentetic acid, 40.24 mg calcium carbonate and NaOH) in water for injection, USP. The pH of the solution is adjusted with NaOH and is between 7.3-8.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In a study of rodents internally contaminated with plutonium, the rate of plutonium elimination was measured after treatment with Ca-DTPA and Zn-DTPA given intravenously as a single dose of 10 to 1,000 micromol/kg (0.54-54 × maximum human dose, MHD). When treated within one hour of internal contamination, Ca-DTPA resulted in about a 10-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, a time period when the radiocontaminant 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, Ca-DTPA had more toxicity (e.g., more depletion of trace metals, higher rate of

mortality, the presence of kidney and liver vacuolization, and 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 micromol/kg (0.11 MHD) 30 minutes after contamination followed by inhalation of Zn-DTPA 2 micromol/kg at approximately 6 hours, 1, 2, 3, and 6 days, then twice weekly to day 26 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.

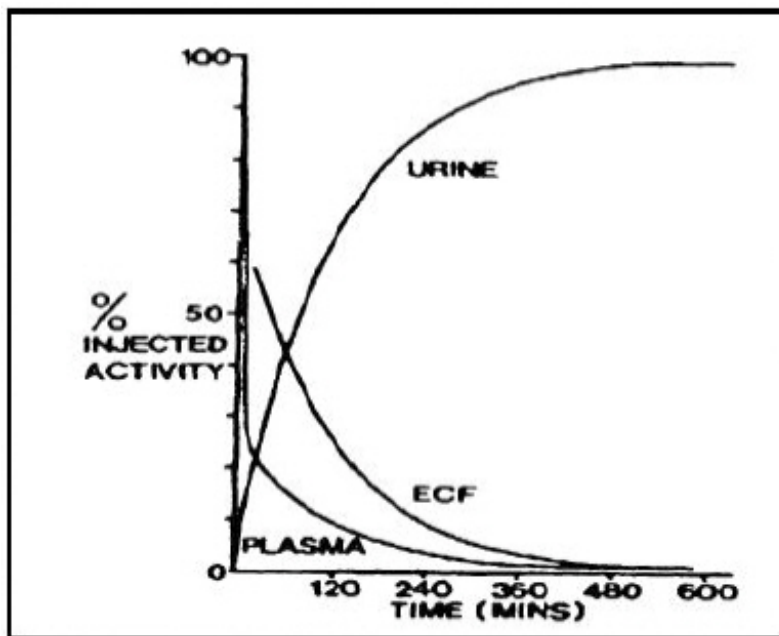
Literature and U.S. Registry data in humans indicate that intravenous administration of Ca-DTPA forms chelates with radioactive contaminants found in the circulation, interstitial fluid, and tissues. When Ca-DTPA is administered by inhalation within 24 hours of internal radioactive contamination, it can chelate transuranium elements. Expectoration is expected to decrease the amount of radioactive contaminant available for systemic absorption.

The effectiveness of chelation decreases with time after internal contamination because the transuranium elements become incorporated into the tissues. Give chelation treatment as soon as possible after known or suspected internal contamination with transuranium elements has occurred. [See *Dosage and Administration (2.1, 2.2)*]

12.3 Pharmacokinetics

Plasma retention and urinary excretion data were obtained in 2 subjects that received 750 kBq of ^{14}C -DTPA. As shown in Figure 1, the radiolabeled DTPA was rapidly distributed throughout the extracellular fluid space and was cleared by glomerular filtration. The plasma retention up to 7 hours post dosing was expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection 24 hours after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, cumulative urinary excretion was more than 99% of the injected dose.

Figure 1: Percent of ^{14}C -DTPA Distribution



Absorption

Ca-DTPA is poorly absorbed in the gastrointestinal tract. In animal studies, after oral administration, absorption was approximately 5%. In a U.S. Registry of 18 patients who received a single inhaled or intravenous dose of 1 gram, urine data indicate that the inhaled product was absorbed and resulted in a comparable elimination of the radiocontaminant. One study of 2 human subjects that received Ca-DTPA with ^{14}C -DTPA by inhalation revealed approximately 20% absorption from the lungs. Human or animal

bioavailability comparisons for Ca-DTPA are not available after administration by inhalation and intravenous injection. [See *Clinical Studies (14)*]

Distribution

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

Metabolism

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

Adverse Metabolic Effects

Studies in animals and humans showed that Ca-DTPA binds endogenous metals of the body (i.e., zinc (Zn), magnesium (Mg) and manganese (Mn)). In an animal study, high doses of Ca-DTPA led to the loss of zinc and manganese mainly from the small intestine, skeleton, pancreas, and testes. Dosing over several days resulted in mobilization or binding of endogenous metals in exchange for calcium and a consequent impairment of metal-controlled or activated systems. The rate and amount of endogenous metal depletion increased with split daily dosing and with the length of treatment. Depletion of these endogenous metals can interfere with necessary mitotic cellular processes. Over longer time periods, depletion of zinc due to Ca-DTPA therapy may result in transient inhibition of a metalloenzyme- δ -aminolevulinic acid dehydrase (ALAD) in the blood and suppressed hematopoiesis.

Elimination

Ca-DTPA is cleared from the plasma in the first few hours after dosing through urinary excretion by glomerular filtration. Renal tubular excretion has not been documented. In stool samples tested, only a very small amount of radioactivity (<3%) was detected.

Renal Impaired and/or Compromised Liver Function Patients

Adequate and well-controlled pharmacokinetic and pharmacodynamic studies in renally impaired and/or hepatically impaired patients were not identified in the literature. Both Ca-DTPA and its radioactive chelates are excreted by glomerular filtration. Impaired renal function may decrease their rates of elimination and increase the serum half-life of Ca-DTPA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Ca-DTPA to evaluate carcinogenesis, mutagenesis, and impairment of fertility have not been performed. Data for Ca-DTPA effects on spermatogenesis are not available.

13.2 Animal Toxicology and/or Pharmacology

[See *Clinical Pharmacology (12)*]

14 CLINICAL STUDIES

All clinical data has come from the treatment of individuals who were accidentally contaminated. Observational data were maintained in a U.S. Registry of individuals with internal radioactive contamination primarily from acute occupational contamination with plutonium, americium, and curium.

In 286 individuals, bioassays were available to measure urinary radioactivity elimination after chelation therapy. Of these 286 individuals, 18 had matched pre- and post-chelator urine radioactivity bioassay results available. Seventeen of these individuals received 1 gram of Ca-DTPA as the first dose. Of these, 9 individuals received the first dose by nebulization (1:1 Ca-DTPA and saline) and 8 received

Ca-DTPA intravenously. The elimination of radiocontaminants was measured using the ratio of the urine radioactivity before treatment to the maximum urine radioactivity after treatment (the excretion enhancement factor, EEF). As shown in Table 1, after one dose, the mean EEF was 25.7. The descriptive results and variability for the intravenous, inhaled, and combined routes are considered to be similar.

Table 1: Urine Excretion Enhancement Factor (EEF) of Transuranium Elements after an Initial Dose of 1g (Ca-DTPA, N=17)

Results	Intravenous	Inhaled	Combined Routes
Mean	25.9	25.4	25.7
Median	12.5	19.3	12.8
SD	33.8	28.2	30.1
Range	1.1-396.1	0.5-80.0	0.5-396.1

After initial treatment with Ca-DTPA, maintenance treatment was continued with 1 gram Zn-DTPA doses over a period of days, months or years, depending upon the extent of internal contamination and individual response to therapy. Most patients received a single dose of Ca-DTPA. The longest treatment duration was approximately 6.5 years. Similar increases in urinary radioactivity elimination following chelator administration were supported by data from the remaining 268 individuals in the U.S. Registry and from the literature.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ca-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 calcium trisodium.

NDC 70651-001-03: 5 mL single-dose ampoules, package of 10.

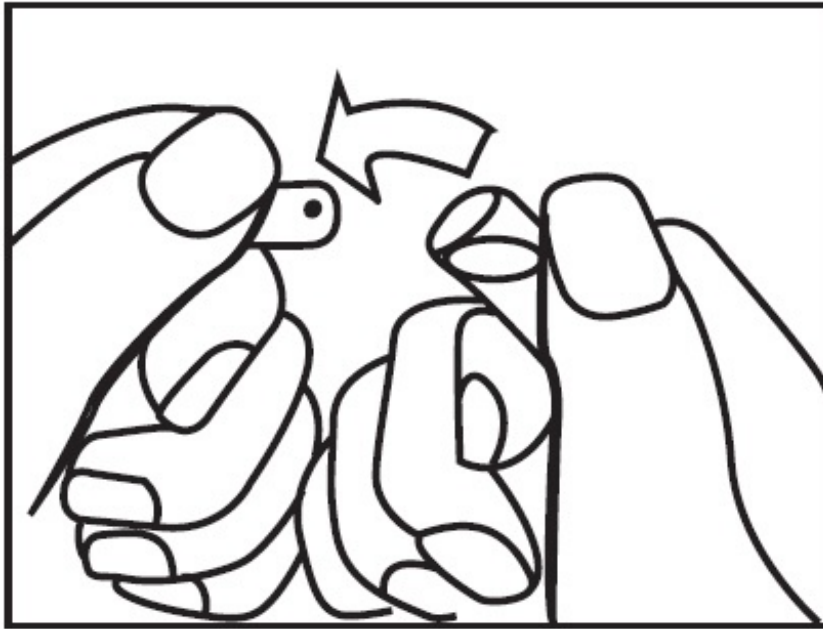
16.2 Storage

Store between 15-30°C (59-86°F).

16.3 Handling

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The product may be filtered using a sterile filter if particles are seen subsequent to opening of the ampoule.

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



17 PATIENT COUNSELING INFORMATION

Instruct patients to:

- drink plenty of fluids and void frequently to promote dilution of the radioactive chelate in the urine and minimize radiation exposure directly to the bladder.
- use a toilet instead of a urinal, and flush several times after each use.
- clean up spilled urine or feces completely and wash hands thoroughly. Wash clothing or linens separately if blood or urine comes in contact.
- dispose of any expectorant carefully. Avoid swallowing the expectorant if possible.

Instruct parents and child-care givers to take extra precaution in handling the urine, feces, and expectorants of children to avoid any additional exposure to either the care-giver or to the child.

Instruct nursing mothers to take extra precaution in disposing of breast milk. [*See Use in Specific Populations (8.3)*]

18 COLLECTION OF PATIENT TREATMENT DATA

To develop long-term response data and information on the risk of developing late malignancy, provide detailed information on patient treatment to the manufacturer (see Patient Treatment Data Form). In case you need additional forms, please use the enclosed form as a template or see the following website: www.ca-dtpa.com. 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 Ca-DTPA for the treatment of internal contamination with transuranium elements may be referred to:

hameln pharmaceuticals ltd
Nexus
Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom
Tel: + 44 / 1452 / 621661
Fax: +44 / 1452 / 632732
e-mail: drugsafety@hameln.co.uk
Contact person: Richard Wysocki

Phone: +44 / 1452 / 621661
Fax: +44 / 1452 / 632732
Email: r.wysocki@hameln.co.uk

Revised: 10/2016

44641/17/16

Ca-DTPA Patient treatment Data

Send to: hameln pharmaceuticals ltd, Nexus, Gloucester Business Park, Gloucester, GL3 4AG, United Kingdom

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
(h/o lung disease, cough, dyspnea, chest tightness, wheezing)? _____
Internal:
 Ca-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

PRINCIPAL DISPLAY PANEL - 5 mL Ampoule Package

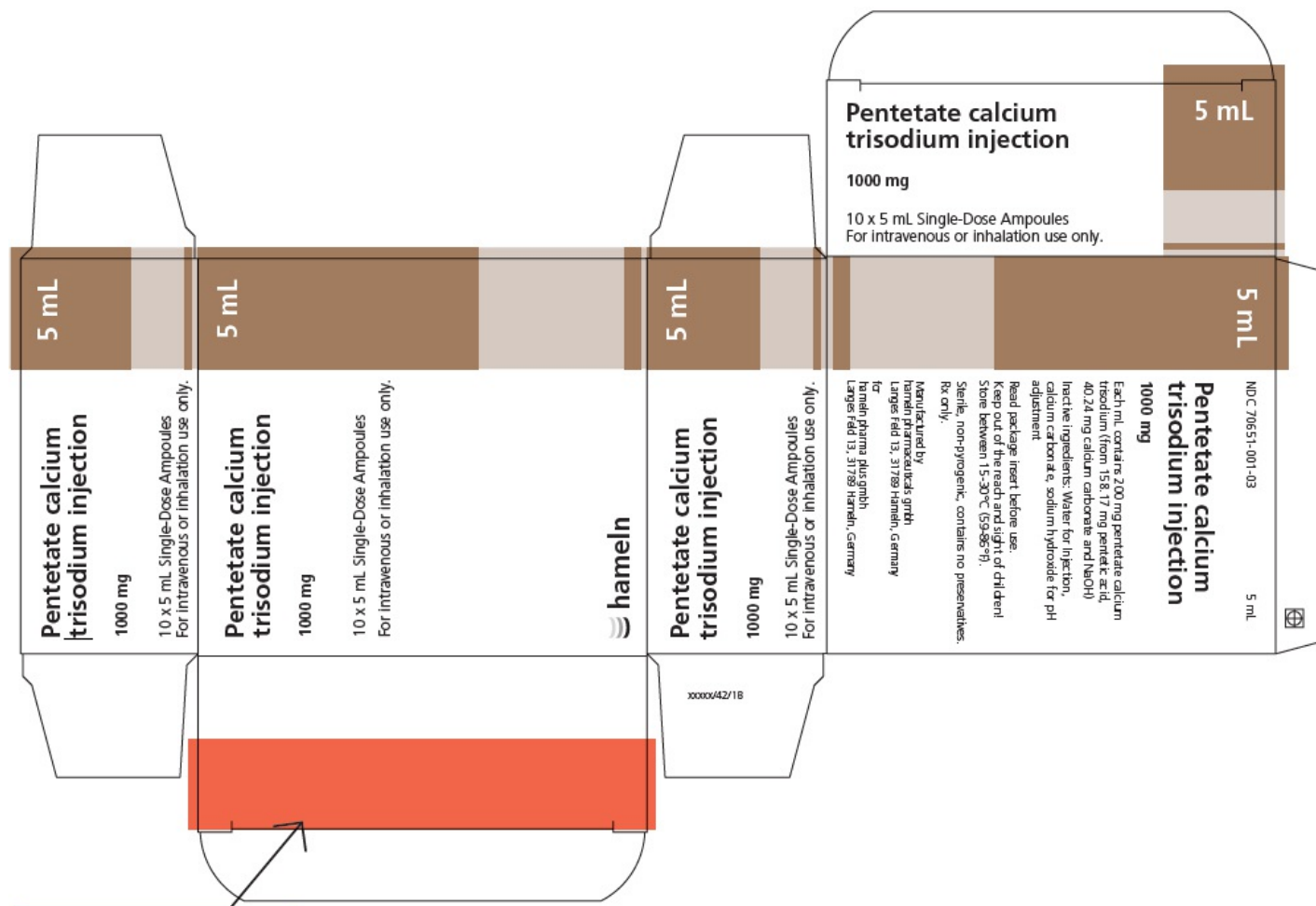
Pentetate calcium trisodium injection

5 mL

1000 mg

10 x 5 mL Single-Dose Ampoules
For intravenous or inhalation use only.

hameln



Varnish free field for 2D Barcode and Associated information

Batch no:
Exp. date:
PC:
SN:

PENTETATE CALCIUM TRISODIUM			
pentetate calcium trisodium injection, solution, concentrate			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:70651-001
Route of Administration	INTRAVENOUS, RESPIRATORY (INHALATION)		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
pentetate calcium trisodium (UNII: G79YN26H5B) (pentetic acid - UNII:7A314HQM0I)	pentetate calcium trisodium	1000 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
Water (UNII: 059QF0KO0R)	
Sodium hydroxide (UNII: 55X04QC32I)	
Calcium carbonate (UNII: H0G9379FGK)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70651-001-03	10 in 1 PACKAGE	08/11/2004	
1		5 mL in 1 AMPULE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021749	08/11/2004	

Labeler - hameln pharma plus gmbh (319361341)**Establishment**

Name	Address	ID/FEI	Business Operations
Siegfried Hameln Gmbh		315869123	MANUFACTURE(70651-001) , LABEL(70651-001) , ANALYSIS(70651-001) , PACK(70651-001)

Revised: 1/2020

hameln pharma plus gmbh