Guidance for Industry

Calcium DTPA and Zinc DTPA Drug Products — Submitting a New Drug Application

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)

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Clinical Medical

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Contains Nonbinding Recommendations

Guidance for Industry[1] Calcium DTPA and Zinc DTPA Drug Products — Submitting a New Drug Application

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers wishing to submit new drug applications (NDAs) for pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA) drug products for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium. The *Federal Register* notice announcing the availability of this guidance explains in detail our findings regarding safety and effectiveness and includes a list of the literature on which we partially based those findings.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in our guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diethylenetriaminepentaacetate (DTPA) is a ligand that acts as a chelator with a very high affinity for certain transuranium radioactive elements. The calcium salt of DTPA is known as pentetate calcium trisodium and is referred to as Ca-DTPA.[2] The zinc salt of DTPA is known as

[1] This document was developed in the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

[2] For purposes of this notice Ca-DTPA refers only to pentetate calcium trisodium, which has an empirical formula of $Na_3CaC_{14}H_{18}N_3O_{10}$ and the Chemical Abstracts Service (CAS) registry number 12111-24-9. Zn-DTPA refers only to pentetate zinc trisodium, which has an empirical formula of $Na_3ZnC_{14}H_{18}N_3O_{10}$ and the CAS registry number 125833-02-5.

pentetate zinc trisodium and is referred to as Zn-DTPA. For several decades, Ca-DTPA and Zn-DTPA have been used investigationally to enhance the excretion of transuranium isotopes from the body by means of ion exchange, chelation, and, ultimately, excretion through the urine. DTPA has a very high affinity for transuranium elements. The calcium or zinc ions of the Ca-DTPA and Zn-DTPA drugs are readily exchanged for the transuranium isotopes, and the transuranium-DTPA complex is rapidly excreted in the urine.

Ca-DTPA and Zn-DTPA in sterile aqueous solution have been used under investigational new drug applications (INDs) held by the Radiation Emergency Assistance Center/Training Site (REAC/TS). REAC/TS is part of the Oak Ridge Associated Universities (ORAU). ORAU operates the Oak Ridge Institute for Science and Education (ORISE) under a contract with the Department of Energy. The INDs are for treatment of contamination resulting from nuclear power or other industrial accidents.

REAC/TS has retained the medical case reports on 646 patients treated with Ca-DTPA and Zn-DTPA for radiation contamination during the last 40 years. To facilitate the development and ultimate approval of Ca-DTPA and Zn-DTPA drug products, we received permission to obtain and review the medical reports on the patients in the REAC/TS database. We also reviewed the related available published literature.

After reviewing the REAC/TS database and the published literature, we have concluded that Ca-DPTA and Zn-DTPA drug products, when produced under conditions specified in approved NDAs, can be found to be safe and effective for treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

III. NDAs SUBMITTED FOR Ca-DTPA AND Zn-DTPA DRUG PRODUCTS

A. Types of NDAs for Ca-DTPA and Zn-DTPA

An NDA for a Ca-DTPA or Zn-DTPA drug product may be either:

- a 505(b)(2) application, which is an NDA in which you rely for approval on studies that you did not conduct, that were not conducted for you, or for which you do not have a right of reference (described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(b)(2))

or

- a 505(b)(1) application, an NDA that relies exclusively on studies that you conducted, that were conducted for you, or for which you have a right of reference (submitted under section 505(b)(1) of the act)

After an NDA for a Ca-DTPA or Zn-DTPA drug product has been approved, abbreviated new drug applications (ANDAs) that refer to the approved Ca-DTPA or a Zn-DTPA drug product can be submitted and approved (see 21 CFR part 314, subpart C). Because ANDAs cannot be

submitted until an NDA is approved, we primarily discuss 505(b)(1) and 505(b)(2) applications in this guidance.

1. Submitting 505(b)(2) Applications

If you rely on published literature (including the literature we have already reviewed, see the *Federal Register* notice announcing the availability of this guidance) and our evaluation of the REAC/TS data for approval of your application, your NDA will be a 505(b)(2) application.

A 505(b)(2) application could be considered the more direct and, probably, the quickest approach to gaining approval of an NDA for a Ca-DTPA or a Zn-DTPA drug product. A 505(b)(2) application could rely entirely on the published literature that we have already reviewed and our evaluation of the REAC/TS data for the clinical data required for approval of an NDA (see the *Federal Register* notice announcing the availability of this guidance). If you took this approach to approval, you would not need to submit copies or summaries of the reports we have cited. The clinical sections of your NDA would only have to cite the *Federal Register* notice and the listed reports we relied on in making our determination of safety and effectiveness.

2. Submitting 505(b)(1) Applications

As mentioned above, you can also submit a 505(b)(1) application. This type of NDA relies only on studies that you have conducted, that were conducted for you, or for which you have a right of reference. These NDAs are sometimes called *full NDAs* and are the type of application most frequently used to gain approval for drug products whose active ingredient is not in a previously approved drug product.

We recognize the importance of continuing the development of products, such as Ca-DTPA and Zn-DTPA drug products, to treat or prevent radiation and other types of toxicity. We also recognize that you might not be able to conduct definitive human efficacy studies for Ca-DTPA and Zn-DTPA because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic substance, and new field trials to study Ca-DTPA and Zn-DTPA efficacy after an accidental or hostile exposure to a transuranium radioactive element might be infeasible. We encourage persons who wish to submit 505(b)(1) applications for Ca-DTPA and Zn-DTPA drug products to contact us, before starting any studies, to discuss the development of data to establish safety and effectiveness.

B. Content of NDAs for Ca-DTPA and Zn-DTPA

NDAs submitted to the Agency for approval must include chemistry, manufacturing, and controls information. They must also contain labeling and the appropriate patent information. These requirements are contained primarily in § 314.50.

1. Chemistry, Manufacturing, and Controls Information

In addition to the clinical data discussed in the *Federal Register* notice announcing the availability of this guidance, your NDA must also include a complete chemistry, manufacturing, and controls section describing the composition, manufacture, and specification of the drug substance and drug product (section 355(b)(1) of the act and § 314.50). You also must meet all other applicable requirements regarding the content of an NDA (section 355(b)(1) of the act and § 314.50).

2. Labeling for Ca-DTPA and Zn-DTPA

We have prepared draft labeling for 1 g of Ca-DTPA in 5 mL of sterile aqueous solution for intravenous or inhalation administration and 1 g of Zn-DTPA in 5 mL of sterile aqueous solution for intravenous administration. You can use this labeling as part of a 505(b)(2) application for Ca-DTPA or Zn-DTPA drug products. This draft labeling reflects our conclusion on the potential safety and effectiveness of Ca-DTPA and Zn-DTPA drug products for treatment of patients with known or suspected internal contamination with plutonium, americium, or curium, to increase the rates of elimination. The draft labeling may need to be modified if you submit an NDA for either Ca-DTPA or Zn-DTPA and there is not an approved NDA for the other DTPA drug product, or the other drug product is otherwise unavailable. If you wish to change the labeling to include a different or broader indication or different dosage, or if you wish to make any other significant changes to the draft labeling, you should provide, as part of your 505(b)(2) application, additional literature or other studies to support your requested changes. If you submit a 505(b)(1) application for a Ca-DTPA or Zn-DTPA drug product, you may not use the draft labeling we have prepared because it is based on our review of the published literature and the REAC/TS data. If you submit a 505(b)(1) application for Ca-DTPA or Zn-DTPA, your labeling must be based on the data contained in your NDA (section 355(b)(1) of the act and § 314.50).

The draft labeling for 505(b)(2) applications is available on the Internet.[3] You can also contact the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7510, for a copy of the draft labeling.

3. Patent Information

If you submit an NDA (including a 505(b)(2) NDA) for either Ca-DTPA and Zn-DTPA, you must file with your NDA a complete patent declaration form (Form FDA 3542a) for each patent that is required to be submitted under section 355(b)(1)(F) of the act and §§ 314.50 and 314.53. You also must submit an additional patent declaration form (Form FDA 3542) within 30 days of approval of your NDA or, in the case of newly issued patents, within 30 days of issuance of the patent (section 355(c)(2) of the act and §§ 314.50 and 314.53). If your NDA is approved, we will publish the patent information in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*).

We publish information regarding patents and exclusivity periods for approved drug products in the *Orange Book*. This information is important if you are considering submitting ANDAs or

[3] See http://www.fda.gov/cder/drug/infopage/dtpa/default.htm.

505(b)(2) applications for Ca-DTPA and Zn-DTPA drug products. If a drug product listed in the *Orange Book* has listed patents, the 505(b)(2) application or ANDA seeking to rely on the finding of safety or effectiveness for that listed drug must contain certifications regarding those patents (see § 314.50(i) for 505(b)(2) applications, and § 314.94(a)(12) for ANDAs).

C. Exclusivity

In addition to the protection provided by patents issued by the U.S. Patent and Trademark Office, Ca-DTPA and Zn-DTPA drug products approved by us may be protected from competition by periods of marketing exclusivity that are administered by us. The act provides for periods of marketing exclusivity that prevent us from filing or approving 505(b)(2) applications or ANDAs for drug products that contain the same active moiety[4] as certain previously approved drug products. The active moiety of a Ca-DTPA or Zn-DTPA drug product would be the diethylenetriaminepentaacetate (DTPA) ligand.

The following summaries of marketing exclusivity and orphan drug exclusivity are provided solely for the general information of manufacturers considering submitting an NDA for a Ca-DTPA and Zn-DTPA drug product. They should not be read as statements of our general policy regarding marketing exclusivity and orphan drug exclusivity. Our policy can be found in the regulations cited in this guidance.

1. Five-Year Marketing Exclusivity

A 5-year period of marketing exclusivity is provided by section 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the act when a sponsor obtains approval of an NDA for which no active moiety has been previously approved by the FDA. The 5-year period of marketing exclusivity generally prohibits us from filing a 505(b)(2) application or receiving an ANDA for a drug product that contains the same active moiety as the first drug product containing the active moiety to be approved.[5] The 5-year period of marketing exclusivity begins on the approval date of the first NDA approved for a drug product containing the active moiety. Both 505(b)(1) and 505(b)(2) applications may be entitled to benefit from 5-year marketing exclusivity, but only 505(b)(2) applications and ANDAs are blocked by 5-year marketing exclusivity.

Because we have never approved a drug product that contains the DTPA ligand as the active moiety, the first NDA approved that contains the DTPA ligand as the active moiety will likely receive 5 years of marketing exclusivity. If an NDA containing the DTPA ligand as the active moiety is entitled to 5-year exclusivity, we cannot file[6] a subsequent 505(b)(2) application for a Ca-DTPA or Zn-DTPA drug product for 5 years after the approval date of that NDA. If you

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[4] *Active moiety* is defined in 21 CFR 314.10(a) as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

[5] An exception to the 5-year period permits an applicant to submit a 505(b)(2) application or ANDA after 4 years if it contains a certification of invalidity or noninfringement for a patent listed for the approved drug.

[6] Our regulations regarding filing an NDA and receiving an ANDA are found at 21 CFR 314.101.

have submitted an essentially complete 505(b)(2) application before we approve the first NDA for a Ca-DTPA or Zn-DTPA drug product, review and approval of your 505(b)(2) application would not be blocked by the marketing exclusivity obtained by the first Ca-DTPA or Zn-DTPA drug product approval (54 FR 28872 at 28901, July 10, 1989). However, after we have approved the first NDA for a Ca-DTPA or Zn-DTPA drug product, 5-year marketing exclusivity would prohibit us from filing your 505(b)(2) application, no matter how soon after the first approval we received your application.

2. Three-Year Exclusivity

A 3-year period of marketing exclusivity may be applicable to Ca-DTPA and Zn-DTPA drug products sometime in the future. Three-year marketing exclusivity is provided by section 505(c)(3)(D)(iii) and (j)(5)(D)(iii) of the act. Drug products whose active moiety is the same active moiety as that in a previously approved drug product are entitled to 3-year exclusivity if a new clinical study (other than a bioavailabilty or bioequivalence study) is needed for their approval. If a drug product, or change to a drug product, is given 3 years of exclusivity, we are barred for 3 years from approving any 505(b)(2) application or ANDA for the same drug product, or change to the product, that was granted exclusivity. For example, if an applicant obtains 3 years of exclusivity for a new dosage form of Ca-DTPA or Zn-DTPA, FDA may not approve a 505(b)(2) application or an ANDA for that dosage form of Ca-DTPA or Zn-DTPA for 3 years. However, we can approve a 505(b)(2) application or an ANDA for any previously approved dosage form not protected by the exclusivity.

Our regulations in § 314.108 provide more details on marketing exclusivity. If you are interested in how marketing exclusivity could affect your NDA for Ca-DTPA or Zn-DTPA, you are encouraged to discuss the issue with the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products. If you believe your drug product is entitled to marketing exclusivity, you must submit supporting information in your NDA (§ 314.50(j)).

3. Orphan Drug Exclusivity

In addition to 3- or 5-year marketing exclusivity, orphan drug exclusivity may apply to Ca-DTPA or Zn-DTPA drug products approved for orphan indications. Obtaining orphan drug exclusivity is a two-step process. The regulations require that you seek orphan drug designation for the active moiety of your drug product for an orphan indication before you submit an NDA. If we designate the drug as an orphan drug and then approve it for the designated indication, the drug will receive orphan drug exclusivity. The issues involved in determining which drug products are entitled to orphan drug exclusivity and which drug products are blocked by orphan drug exclusivity are described in our regulations in part 316 (21 CFR part 316). However, we note that orphan drug exclusivity is for a 7-year period and can prohibit us from approving a 505(b)(1) application, a 505(b)(2) application, or an ANDA for the same active moiety for the same indication during the period of exclusivity. This differs from 5-year marketing exclusivity, which prohibits us from filing a 505(b)(2) application or receiving an ANDA, but would not prohibit us from filing a 505(b)(1) application.

4. Waiver of Exclusivity

If you are entitled to any type of exclusivity for a Ca-DTPA or Zn-DTPA drug product, you may waive that exclusivity after approval of your NDA. Your waiver would allow one or more applicants to submit applications for the product. For example, if you obtain 5-year exclusivity with a 505(b)(2) application for a Ca-DTPA or Zn-DTPA drug product, your complete waiver of such exclusivity would enable other applicants to immediately submit 505(b)(2) applications and ANDAs for drug products containing Ca-DTPA or Zn-DTPA.

D. Innovative Ca-DTPA and Zn-DTPA Drug Products

We encourage the development of drug products containing Ca-DTPA or Zn-DTPA for the treatment of internal contamination with transuranium elements that represent improvements in safety, effectiveness, or convenience. However, your submission of a 505(b)(2) application for such an innovative product may be blocked by marketing exclusivity if the exclusivity is not waived. If the innovative product is clinically superior to the previously approved drug product, its approval might not be blocked by orphan drug exclusivity (see § 316.3(b)(13)). Once approved, an innovative product may qualify for 3-year marketing exclusivity. If a subsequent drug product represents an innovation that presents a commercial advantage over the drug product that enjoys marketing exclusivity, it may be possible to reach an agreement with the person holding the exclusivity to allow marketing of the subsequent drug product.

Ca - DTPA labeling

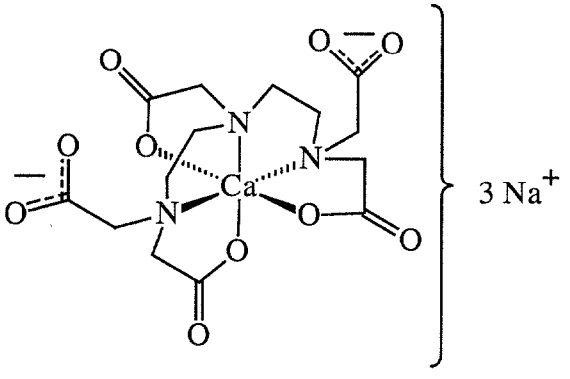
August 28 DRAFT

[Insert trade name_____]
Ca-DTPA (*pentetate calcium trisodium injection*)

For Intravenous or Inhalation Administration

DESCRIPTION

Pentetate calcium trisodium is the sodium salt of calcium diethylenetriaminepentaacetate. The pentetate calcium trisodium is also known as trisodium calcium diethylenetriaminepentaacetate and is referred to as Ca-DTPA. It has a molecular formula of $Na_3CaC_{14}H_{18}N_3O_{10}$ and a molecular weight of 497.4 daltons. The drug is supplied as 1 gram in 5 ml of sterile aqueous solution. [*Insert any inactive ingredients.*] The structural formula is shown below.



CLINICAL PHARMACOLOGY

General

Ca-DTPA forms stable chelates with metal ions by exchanging calcium for a metal of greater binding capacity. DTPA has a very high affinity for certain transuranium radioactive elements (e.g., plutonium, americium, curium, berkelium and californium). The radioactive chelates are then excreted by glomerular filtration into the urine.

Ca-DTPA forms less stable chelates with uranium and neptunium in vivo resulting in the deposition of these elements in tissues including the bone in animal studies. Ca-DTPA treatments are not expected to be effective for uranium and neptunium. Radioactive iodine is not bound by DTPA.

Pharmacodynamics

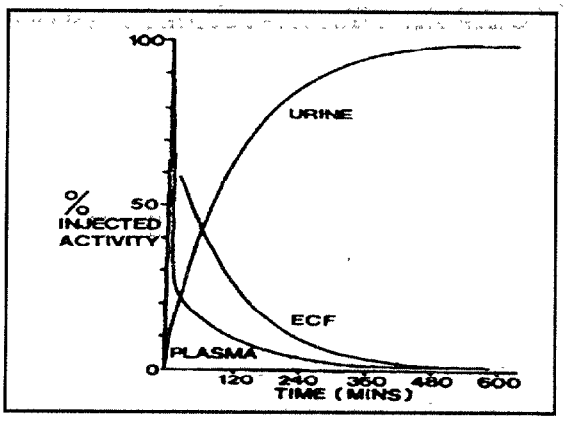
In a study of rodents after exposure to plutonium, the rate of plutonium elimination was measured after treatment with Ca-DTPA and Zn-DTPA given intravenously as a single dose of 10 to 1,000 μmol/kg (0.54 – 54 x MHD). In this study, when treated within one hour of plutonium exposure, in comparison to Zn-DTPA, treatment with Ca-DTPA resulted in about a 10 fold higher rate of urinary chelate elimination. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after exposure when the radioactive contaminant 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 radiation elimination. 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).

Literature and U.S. Registry data indicate that intravenous administration of Ca-DTPA forms chelates with radiation contaminants found in the circulation, interstitial fluid, and tissues. When Ca-DTPA is administered by inhalation within 24 hours of radiation exposure, it can chelate particulate transuranium elements. Expectoration of these is expected to decrease the amount of radiation available for systemic absorption. Administration by inhalation is associated with respiratory adverse events in susceptible patients. The effectiveness of chelation decreases with time after contamination because the transuranium elements become incorporated into the tissues. Chelation treatment should be given as soon as possible after known or suspected transuranium element contamination has occurred. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

Pharmacokinetics

Plasma retention and urinary excretion data were obtained in 2 patients that received 750 kBq of ^{14}C-DTPA. As shown in figure 1, the radiolabeled DTPA was rapidly distributed through the extracellular 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 hrs after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, the cumulative urinary excretion was more than 99% of injected dose.

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



Absorption

Ca-DTPA is poorly absorbed by the GI tract. In animal studies, after oral administration, the absorption was approximately 5%.

In a U.S. Registry of 18 patients who received a single inhaled or intravenous dose of 1 gram, the urine data indicate that the inhaled product was absorbed and resulted in a comparable elimination of the radiologic contaminant. One study of 2 human subjects that received Ca-DTPA with ^{14}C-DTPA by oral inhalation revealed approximately 20% absorption from the lungs. Human or animal bioavailability comparisons for Ca-DTPA are not available after administration by inhalation and injection (intravenous, intramuscular or intraperitoneal). (See **CLINICAL PHARMACOLOGY, Clinical Trials**.)

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 with radioactivity marked chelating agents, 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.

Clinical Trials

Observational data was maintained in a U.S. Registry of patients with radiation contamination primarily from acute occupational exposure to plutonium, americium, and, curium.

In 286 patients, bioassays were available to measure urinary radiation elimination after chelation therapy. Of these 286 patients, only 18 had matched pre-and post-chelator urine radiation bioassay results available. Seventeen of these patients received the first dose of chelator as Ca-DTPA 1 gram. Of these, 9 patients received the first dose as 1 gram by nebulization (1:1 Ca-DTPA and saline) and 8 received 1 gram of Ca-DTPA intravenously. The elimination of radioactive elements 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 both routes are considered to be similar.

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

Results	Intravenous	Inhaled	Both 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 with Zn-DTPA 1-gram was given over a period of days, months or years, depending upon the amount of contamination. In most patients the dosing interval was daily after the initialdose. It decreased to weekly and monthly. Treatment was generally continued until the EEF approached 1. The longest treatment duration was approximately 4 years.

Similar increases in urinary radiation elimination following chelator administration were supported by data from the remaining 268 patients in the U.S. Registry and from the literature.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None known.

WARNINGS

Ca-DTPA is associated with depletion of endogenous metals (e.g., zinc, magnesium, manganese). The magnitude of depletion increases with administration of more than one dose per day, increasing dose, and increased treatment duration. Only a single initial dose of Ca-DTPA is recommended. The dose should not be divided because it increases the rate of endogenous metal depletion. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism***). After the initial dose, on the next day chelation therapy can continue with CA-DTPA. However, it is preferable to switch to Zn-DTPA, if available, for continued treatment after the initial dose of Ca-DTPA. (See **Zn-DTPA labeling**)

Ca-DTPA administered by nebulized inhalation may be associated with exacerbation of asthma and anaphylaxis in patients with a history of respiratory disorders. Caution should be exercised when administering Ca-DTPA by the inhalation route. (See **ADVERSE REACTIONS.**)

Ca-DTPA is administered to decrease internal contamination with certain transuranic radioactive isotopes. It does not treat the complications of radiation exposure. Patients contaminated with high levels of transuranium radioactive elements may develop radiation toxicity including bone marrow suppression with severe neutropenia and thrombocytopenia. As appropriate, supportive treatment for radiation toxicity should be given concomitantly with Ca-DTPA.

In radiologic emergencies, the radionuclide may not be known. Ca-DTPA may not bind to all radioactive elements. Patients contaminated with unknown or multiple radioactive elements may require concomitant treatment with other therapies in addition to Ca-DTPA (e.g., potassium iodide and Prussian blue).

PRECAUTIONS

General*: Metabolic*

Treatment over several days with Ca-DTPA could lead to depletion of body stores of zinc, magnesium and manganese. Prolonged treatment may result in depletion of zinc containing metalloenzymes necessary for DNA synthesis and hemoglobin production. These elements should be monitored closely and, as appropriate, mineral or vitamin plus mineral supplements that contain zinc should be provided.

Information for Patients

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with these radioactive isotopes, Ca-DTPA treatment increases excretion of radioactivity in the urine (by as much as a factor of 100 over pre-treatment levels). This high concentration may persist for several days after Ca-DTPA is given. Appropriate safety measures should be taken to minimize radiation exposure to others. When possible, a toilet should be used instead of a urinal, and it should be flushed several times after each use. Spilled urine or feces should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine comes in contact with clothing or linens, they should be washed separately. Patients should drink plenty of fluids and void frequently.

If patients are coughing, any expectorant should be disposed of carefully. Swallowing the expectorant should be avoided if possible.

Parents and child-care givers should take extra precaution in handling the urine, feces, and expectorants of pediatric patients, to avoid any additional exposure to either the care-giver or to the pediatric patient.

Nursing mothers should take extra precaution in disposing of breast milk. (See **PRECAUTIONS, Nursing Mothers.**)

Laboratory Tests

Serum electrolytes and essential metals should be closely monitored during Ca-DTPA treatment. Mineral or vitamin plus mineral supplements that contain zinc should be given as appropriate. (See **WARNINGS** and **PRECAUTIONS.**)

Drug-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 radioactive isotopes, or when the radioactive contaminants are unknown, Ca-DTPA can be co-administered with other radioprotectants (e.g., Prussian blue, potassium iodide).

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.

Teratogenic Effects: *Pregnancy Category C*

There are no human pregnancy outcome data from which to assess the risk of Ca-DTPA exposure on fetal development. Ca-DTPA is believed to be teratogenic based on animal data and because chelation and depletion of body stores of zinc is known to affect DNA and RNA synthesis in humans. Multiple doses of Ca-DTPA could result in higher risk for adverse reproductive outcome. Therefore, multiple doses of Ca-DTPA are not recommended in pregnancy. In cases of high levels of radiation contamination, if Zn-DTPA is not available, the teratogenic risks of administering multiple doses of Ca-DTPA should be weighed against the risks of early and late radiation toxicity.

There are no animal or human data evaluating the teratogenic effect of the administration of a single dose of Ca-DTPA. Based on its mechanism of action, the likelihood that a single dose of Ca-DTPA is teratogenic in humans cannot be ruled out. Therefore, treatment of pregnant women should begin and then continue with Zn-DTPA, if available, except in cases of high radiation

contamination. In cases of high radiation contamination, the risk of immediate and delayed radiation-induced toxicity to both the mother and the fetus should be considered in comparison to the risk of Ca-DTPA toxicity. In these cases, it may be appropriate to use a single dose of Ca-DTPA with vitamin or mineral supplements that contain zinc as the initial treatment because Ca-DTPA is more effective than Zn-DTPA in the first 24 hours after contamination.

Ca-DTPA has been shown to be teratogenic and embryocidal in mice following five daily injections of 720-2880 µmol Ca-DTPA/kg [2- 8 times the recommended daily human dose of 1 gram based on body surface area (BSA) adjusted dose] given during any period of gestation. The frequency of gross malformation (e.g., exencephaly, spina bifida, and cleft palate) increased with dose, with higher susceptibility in early and mid gestation Five daily doses of 360 µmol Ca-DTPA/kg in mice, approximately equivalent to the recommended daily human dose (based on BSA) produced no harmful effects. Studies of 2 pregnant beagles given daily injections of Ca-DTPA at 30 µmol/kg, (approximately half the recommended daily human dose based on BSA) from implantation until parturition showed severe teratogenic effects (especially brain damage).

Nursing Mothers

Studies to determine if Ca-DTPA is excreted in breast milk have not been conducted.

Radioactive elements are known to be excreted in breast milk. Women with known or suspected internal contamination with radioactive isotopes should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. (See **PRECAUTIONS, Information for Patients**.)

Pediatric Use

The safety and efficacy of Ca-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population on the basis of the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an intravenous drug that is renally cleared.

ADVERSE REACTIONS

In the U.S. database, a total of 646 patients received at least one dose of either Ca-DTPA or Zn-DTPA. Of these, 632 received Ca-DTPA. For the 632 patients that received Ca-DTPA, 326 patients were dosed by inhalation, 293 by intravenous injection, and 60 by other or unknown routes of administration.

Of the patients that received Ca-DTPA, 393/632 (62%) received one dose. The largest number of dosing treatments for Ca-DTPA was 338. In the literature, prolonged treatment with Ca-DTPA resulted in depletion of zinc, magnesium, manganese and possibly metalloproteinases.

Overall, the presence or absence of adverse events was recorded in 310/646 patients. Of these 19 (6.1%) patients 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.

These events included headache, lightheadedness, chest pain, acute cough or wheezing, allergic reaction, dermatitis, metallic taste, nausea and diarrhea, injection site reactions.

Two individuals experienced cough and/or wheezing with the nebulized inhalation of Ca-DTPA.

OVERDOSAGE

Overdose with Ca-DTPA has not been reported. Based upon the mechanism of action, symptoms of endogenous metal depletion may occur. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*, WARNINGS, and PRECAUTIONS**.)

DOSAGE AND ADMINISTRATION

THE MAIN OBJECTIVE OF CHELATION TREATMENT IS TO REDUCE INTERNAL RADIOACTIVE CONTAMINATION BY INCREASING THE RATE OF EXCRETION AND REDUCING TISSUE DEPOSITION.

Treatment should be started as soon as possible after suspected or known contamination. However, even when treatment cannot be started right away, patients should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following exposure.

If contamination with isotopes other than plutonium, americium, or curium, or with unknown isotopes is suspected, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

The chelating effect of Ca-DTPA is greatest when the radionuclide is still circulating or is in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radionuclide becomes sequestered in liver and bone.

Patients should 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.

Initial dose

Adults and adolescents: A single 1.0 gram loading dose of Ca-DTPA administered intravenously.

Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously. The maximum single loading dose should not exceed 1.0 gram.

Renally impaired patients: No dose adjustment is needed. However, in heavily contaminated patients 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

After the initial dose, on the next day chelation therapy can continue with Ca-DTPA. However, due to safety concerns associated with prolonged Ca-DTPA use, it is preferable to switch to Zn-DTPA, if available, for continued treatment after the initial dose of Ca-DTPA. (See **Zn-DTPA labeling**)

Adults and adolescents: The recommended maintenance dose of Ca-DTPA is 1.0 gram once a day administered intravenously.

Pediatrics (less than 12 years of age): The recommended maintenance dose of Ca-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. However, in heavily contaminated patients 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.

Treatment should continue for a minimum of 30 days and then the patient should be reassessed for the amount of residual whole body radioactivity. The duration of treatment after exposure is dictated by the level of contamination and the judgement of the attending physician. Before, during, and after chelation therapy, pertinent measurements for radioactivity should be made to help determine when to terminate treatment.

Methods of Administration

- Intravenous administration of Ca-DTPA is recommended and should be used if the route of radioactive contamination is not known or if multiple routes of contamination are possible. Ca-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 diluted in 100-250 mL of D_5W, Ringers Lactate, or Normal Saline.

- In patients whose contamination is only by inhalation within the preceding 24 hours, Ca-DTPA can be administered by nebulized inhalation as an alternative route of administration. Ca-DTPA 1 gram should be diluted for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, patients should be encouraged to avoid swallowing any expectorant. Some patients experience respiratory adverse events after nebulization (see **WARNINGS**).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Monitoring

When possible, obtain baseline blood and urine samples (CBC with differential, BUN, serum

chemistries, and electrolytes, urinalysis and blood and urine radioassay) before initiating treatment.

Ca-DTPA must be given with very careful monitoring of serum zinc and complete blood counts and, as appropriate, with vitamin or mineral supplements that contain zinc (see **WARNINGS**). If Ca-DTPA is initially administered by inhalation, maintenance treatment with intravenous Ca-DTPA can continue with vitamin or mineral supplements that contain zinc until intravenous Zn-DTPA is available. As soon as Zn-DTPA is available, Ca-DTPA should be stopped and chelation should continue with intravenous Zn-DTPA.

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, the following information should be collected:

- Measurements of the radioactivity in blood, urine, and fecal samples weekly to monitor the transuranium contaminant elimination rate.
- Record any adverse events from Ca-DTPA.
- CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis measurements should be monitored regularly. If the patient is receiving more than an initial dose of Ca-DTPA, these laboratory tests should be very carefully monitored and the patient should be observed for signs of related enzyme deficiencies. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*.)**

HOW SUPPLIED

Each ampule contains 1.0 gram (2.0 millimoles) of Ca-DTPA in X mL of sterile aqueous solution.

NDC# XXXXX-XXX-XX

Storage

Store at XX–XX°C (YY-YY°F) [See USP Controlled Room Temperature]. Protect from light.

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. 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. Contact the manufacturer for more information

Questions regarding the use of Ca-DTPA for the treatment of contamination with transuranium elements may be referred to

(Insert Name and contact information).....

Zn-DTPA labeling

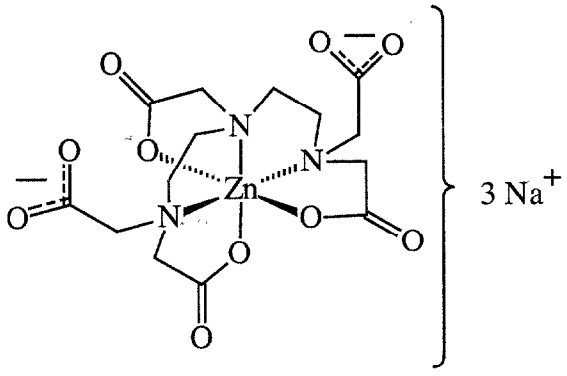
August 28 DRAFT

[Insert tradename _____]
Zn-DTPA (*pentetate zinc trisodium injection)*

For Intravenous Administration

DESCRIPTION

Pentetate zinc trisodium is the sodium salt of zinc diethylenetriaminepentaacetate. The pentetate zinc trisodium is also known as trisodium zinc diethylenetriaminepentaacetate and is referred to as Zn-DTPA. It has a molecular formula of $Na_3ZnC_{14}H_{18}N_3O_{10}$ and a molecular weight of 522.7 daltons. The drug is supplied as 1 grams of complex in 5 ml of sterile aqueous solution. [*Insert any inactive ingredients*] The structural formula is shown below.



CLINICAL PHARMACOLOGY

General

Zn-DTPA forms stable chelates with metal ions by exchanging zinc for a metal of greater binding capacity. DTPA has a very high affinity for certain transuranium radioactive elements (e.g., plutonium, americium, curium, berkelium and californium). The radioactive chelates are then excreted by glomerular filtration into the urine.

Zn-DTPA forms less stable chelates with uranium and neptunium *in vivo* resulting in deposition of these elements in tissues including the bone in animal studies. Zn-DTPA treatments are not expected to be effective for uranium and neptunium. Radioactive iodine is not bound by DTPA.

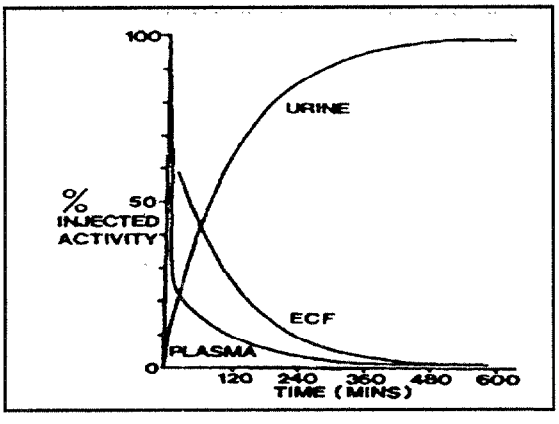
Pharmacodynamics

In a study of rodents after exposure to 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 μmol/kg (0.54 – 54 x MHD). In this study, when treated within one hour of plutonium exposure, in comparison to Zn-DTPA, treatment with Ca-DTPA resulted in about a 10 fold higher rate of urinary chelate elimination. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after plutonium exposure when the radioisotope 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 radiation elimination. 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). The amount of Zn-DTPA chelation is dependent not only on the transuranium element, but also on the chemical and physical characteristics of the transuranium compound at the time of Zn-DTPA administration. The effectiveness of chelation decreases with time after contamination because the transuranium elements become incorporated into the tissues. Chelation treatment should be given as soon as possible after known or suspected transuranium element contamination has occurred. (See **WARNINGS** and **DOSAGE ADMINISTRATION**.)

Pharmacokinetics

Plasma retention and urinary excretion data were obtained in 2 patients that received 750 kBq of ^{14}C-DTPA. As shown in figure 1, the radiolabeled DTPA was rapidly distributed through the extracellular 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 hrs after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, the cumulative urinary excretion was more than 99% of injected dose.

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



Absorption

Zn-DTPA is poorly absorbed by the GI tract. In animal studies, after oral administration, the absorption was approximately 5%.

Human or animal bioavailability comparisons for Zn-DTPA are not available after administration by inhalation and injection (intravenous, intramuscular or intraperitoneal). (See **CLINICAL PHARMACOLOGY, Clinical Trials.**)

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 in 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: Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Zn-DTPA results in minimal depletion of magnesium and manganese.

Elimination

Zn-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 with radioactivity marked chelating agents, 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 Zn-DTPA and its radioactive chelates are excreted by glomerular filtration. Impaired renal function may decrease their rates of elimination.

Clinical trials

Observational data was maintained in a U.S. Registry of patients with radiation contamination primarily from acute occupational exposure to plutonium, americium, and curium.

In 286 patients, bioassays were available to measure urinary radiation elimination after chelation therapy. Of these 286 patients, only 18 had matched pre- and post-chelator urine bioassay results available. The majority of these patients received Ca-DTPA as the initial component to their chelation therapy (see Ca-DTPA labeling). Ca-DTPA was administered as soon as possible after internal contamination with transuranium radionuclides (see Ca-DTPA labeing). When multiple chelator doses were administered over days, the standard of practice was to switch therapy to Zn-DTPA following an initial dose of Ca-DTPA because after 24 hours following exposure, both

chelators were considered equipotent but An-DTPA was considered less toxic. There is very little clinical experience with the administration of Zn-DTPA as the initial dose of chelation therapy.

After initial treatment with Ca-DTPA, maintenance treatment was continued with daily 1-gram Zn-DTPA doses administered over a period of days, months or years, depending on the extent of internal contamination. Most patients were dosed daily after the initial dose. Over time the dosing interval decreased to weekly and monthly. Treatment was generally continued until the EEF [need to define]approached 1. The longest treatment duration was approximately 4 years.

Similar increases in urinary radiation elimination were supported by data from the remaining patients in the U.S. Registry and from the literature.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None known.

WARNINGS

Treatment with Zn-DTPA may decrease the levels of magnesium and manganese measured in the blood. The dose should not be divided because it increases the rate of endogenous metal depletion. (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*.**)

Zn-DTPA is administered to decrease internal contamination with certain transuranic radioactive isotopes. It does not treat the complications of radiation exposure. Patients contaminated with high levels of transuranium radioactive elements may develop radiation toxicity including bone marrow suppression with severe neutropenia and thrombocytopenia. As appropriate, supportive treatment for radiation toxicity should be given concomitantly with Zn-DTPA.

In radiologic emergencies, the radionuclide may not be known. Zn-DTPA may not bind to all radioactive elements. Patients contaminated with unknown or multiple radioactive elements may require concomitant treatment with other therapies in addition to Zn-DTPA (i.e., potassium iodide, Prussian blue).

PRECAUTIONS

General: *Metabolic*

Treatment over several months with Zn-DTPA could lead to depletion of body stores of endogenous metals (e.g., magnesium, manganese). These elements should be monitored routinely and, if appropriate, mineral or vitamin plus mineral supplements that contain zinc should be provided.

Information for Patients

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with these radioactive isotopes, Zn-DTPA treatment increases excretion of radioactivity in the urine (by as much as a factor of 100 over pre-treatment levels). This high concentration may persist for several days after Zn-DTPA is given. Appropriate safety measures should be taken to minimize radiation exposure to others. When possible, a toilet should be used instead of a urinal, and it should be flushed several times after each use. Spilled urine or feces should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine comes in contact with clothing or linens, they should be washed separately. Patients should drink plenty of fluids and void frequently.

If patients are coughing, any expectorant should be disposed of carefully. Swallowing the expectorant should be avoided if possible.

Parents and child-care givers should take extra precaution in handling the urine, feces, and expectorants of pediatric patients to avoid any additional exposure to the either the caregiver or to the pediatric patient.

Nursing mothers should take extra precaution in disposing of breast milk. (See **PRECAUTIONS, Nursing Mothers.**)

Laboratory Tests

Serum electrolytes and essential metals should be closely monitored during Zn-DTPA treatment. mineral or vitamin plus mineral supplements that contain zinc should be given as appropriate. (See **WARNINGS** and **PRECAUTIONS**.)

Drug-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 radioactive isotopes, or when the radioactive contaminants are unknown, Zn-DTPA can be co-administered with other radioprotectants (e.g., Prussian blue, potassium iodide).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Zn-DTPA to evaluate carcinogenesis, mutagenesis and impairment of fertility have not been performed.

Data for Zn-DTPA effects on spermatogenesis are not available.

Teratogenic Effects: ***Pregnancy Category B***

There are no human pregnancy outcome data from which to assess the risk of Zn-DTPA exposure on fetal development. Reproduction studies have been performed in pregnant mice at doses up to 11.5 mmol/kg (31 times the recommended daily dose of 1 gram based on body surface area (BSA) adjusted dose) and have revealed no evidence of impaired fertility or harm to the fetus due to Zn-DTPA. There was a slight reduction in the average birth weight. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. However, the risk of toxicity from untreated transuranium contamination is expected to be greater than any reproductive risk of treatment with Zn-DTPA.

Nursing Mothers

Studies to determine if Zn-DTPA is excreted in breast milk have not been conducted.

Radioactive elements are known to be excreted in breast milk. Women with known or suspected internal contamination with radioactive isotopes should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. (See **PRECAUTIONS, Information for Patients.**)

Pediatric Use

The safety and efficacy of Zn-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population on the basis of the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an intravenous drug that is renally cleared.

ADVERSE REACTIONS

In the U.S. database, a total of 646 patients received at least one dose of either Ca-DTPA or ZN-DTPA. Of these, 62 received Zn-DTPA.

Of the patients that received Zn-DTPA, 49 /62 (65%) received multiple doses. The largest number of dosing treatments for Zn-DTPA was 574 doses delivered over 4 years.

Overall, the presence or absence of adverse events was recorded in 310/646 patients. Of these 19 (6.1%) patients reported at least one adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 1 patient treated with Zn-DTPA reported headache, lightheadedness, and pelvic pain.

OVERDOSAGE

Overdose with Zn-DTPA has not been reported. Based upon the mechanism of action, symptoms

of endogenous metal depletion may occur. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*, WARNINGS and PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION

THE MAIN OBJECTIVE OF CHELATION TREATMENT IS TO REDUCE INTERNAL RADIOACTIVE CONTAMINATION BY INCREASING THE RATE OF EXCRETION AND REDUCING TISSUE DEPOSITION.

Treatment should be started as soon as possible after suspected or known contamination. However, even when treatment cannot be started right away, patients should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following exposure..

If contamination with isotopes other than plutonium, americium, or curium, or with unknown isotopes is suspected, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

The chelating effect of Zn-DTPA is greatest when the radionuclide is still circulating or is in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radionuclide becomes sequestered in liver and bone.

Patients should 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.

Initial dose

It is preferable to administer Ca-DTPA, if available, as the initial dose during the first 24 hours after 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.

Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously. The maximum single loading dose should not exceed 1.0 gram.

Renally impaired patients: No dose adjustment is needed. However, in heavily contaminated patients 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.

Pediatrics (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. However, in heavily contaminated patients, 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.

Treatment should continue for a minimum of 30 days and then the patient should be reassessed for the amount of residual whole body radioactivity. The duration of treatment after exposure is dictated by the level of contamination and the judgement of the attending physician. Before, during, and after chelation therapy, pertinent measurements for radioactivity should be made to help determine when to terminate treatment.

Method of Administration

The intravenous route is recommended. 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 diluted in 100-250 mL of D_5W, Ringers Lactate, or Normal Saline.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Monitoring

When possible, obtain baseline blood and urine samples (CBC with differential, BUN, serum chemistries, and electrolytes, urinalysis and blood and urine radioassay) 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, the following information should be collected:

- Measurements of the radioactivity in blood, urine, and fecal samples weekly to monitor the transuranium contaminant elimination rate.
- Record any adverse events from Zn-DTPA.
- CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis measurements should be monitored regularly. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics, *Metabolism*.**)

HOW SUPPLIED

Each ampule contains 1- gram (2.0 millimoles) of Zn-DTPA in X mL of sterile aqueous

solution.

NDC# XXXXX-XXX-XX

Storage

Store at XX-XX°C (YY-YY°F) [See USP Controlled Room Temperature]. Protect from light.

COLLECTION OF PATIENT TREATMANT 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. 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 contamination with transuranium elements may be referred to:

(Insert Name and contact information).....