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HEALTH AFFAIRS

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MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (M&RA)
ASSISTANT SECRETARY OF THE NAVY (M&RA)
ASSISTANT SECRETARY OF THE AIR FORCE (M&RA)
DIRECTOR, JOINT STAFF

SUBJECT: Policy for Department of Defense Stockpile of Pentetate Calcium Trisodium Injection and Pentetate Zinc Trisodium Injection

The Department of Defense established a stockpile of Pentetate Calcium Trisodium Injection (Ca-DTPA) and Pentetate Zinc Trisodium Injection (Zn-DTPA). The U.S. Food and Drug Administration approved both products as countermeasures for the treatment of internal contamination with the radioactive transuranic elements plutonium, americium, and curium. These countermeasures are for the treatment of individuals exposed to and internally contaminated by a Radiological Dispersal Device or Improvised Nuclear Device.

The attachment provides guidelines for the release, release authority, and use of these radiation countermeasures. My point of contact is Colonel Keith Vesely, Director, Medical Countermeasures, Force Health Protection, and Readiness, who may be reached at (703) 845-3310 and Keith.Vesely@ha.osd.mil.

S. Ward Casscells, MD

Attachment:
As stated

cc:
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Director, Health and Safety, US Coast Guard
Director, Defense Logistics Agency

HA POLICY: 09-005

Health Affairs Policy for Release of Department of Defense Stockpile of Pentetate Calcium Trisodium Injection and/or Pentetate Zinc Trisodium Injection for the Treatment of Individuals Exposed To and Internally Contaminated by a Radiological Dispersal Device or Improvised Nuclear Device

The Department of Defense (DoD) established an initial stockpile of Pentetate Calcium Trisodium Injection (Ca-DTPA) and Pentetate Zinc Trisodium Injection (Zn-DTPA) intravenous medications. These medications are for the treatment of individuals exposed to and internally contaminated by a Radiological Dispersal Device (RDD) or Improvised Nuclear Device (IND). The U.S. Food and Drug Administration (FDA) approved Ca-DTPA and Zn-DTPA as countermeasures for the treatment of individuals with known or suspected internal contamination with the radioactive transuranic elements plutonium, americium, or curium to increase the rates of elimination. Ca-DTPA and Zn-DTPA augment existing DoD medical consequence management capability.

The use of Ca-DTPA and Zn-DTPA at military facilities shall be consistent with the Department of Health and Human Services Radiation Event Medical Management guidelines, (http://www.remm.nlm.gov/index.html). For the purposes of this policy, personnel on military installations shall be considered as "the general public" for purposes of access to countermeasures from the strategic national stockpile or other non-DoD sources, with the exception of institutionalized persons and emergency workers whose duties could involve responding to the release of an RDD/IND or otherwise require them to remain in the emergency planning zone. The Assistant Secretary of Defense (Health Affairs) (ASD (HA)) will review this policy upon any future revision o the Department of Health and Human Services guidance on the use of Ca-DTPA and/or Zn-DTPA.

BACKGROUND

United States (U.S.) military personnel, their families, U.S. Government civilian workers, and U.S. Government contractors may be at risk from terrorist use of specific radioactive transuranic metals (i.e. plutonium - Pu, americium - Am, and curium - Cm) as components of a RDD or "dirty bomb." Terrorists might also use plutonium (Pu) as the fissile material in a failed IND. The internal contamination of victims may occur through inhalation, ingestion, and wounds or burns. Various factors, including the chemical form of the isotope and the pathway of absorption, may influence the treatment method and effectiveness of radiocontaminant removal. When prevention of exposure has failed, treatment may include recapture of the radiocontaminant metals through binding with a chelator (i.e., binding agent). Chelation (i.e., binding) involves the formation of stable ionic complexes, eliminated from the body in urine. Ca-DTPA and Zn-DTPA form less stable chelates with uranium and neptunium in vivo resulting in the deposition of these elements in tissues including the bone. Ca-DTPA and Zn-DTPA treatments are not effective for uranium and neptunium. Neither Ca-DTPA nor Zn-DTPA binds radioactive iodine.

STOCKPILES

Medical treatment facilities (MTF) shall be prepared to function independently for up to 48 hours. MTFs with patient holding capability will maintain a minimum of 10 single dose vials of Ca-DTPA and 5 single dose vials of Zn-DTPA. MTF commanders may increase the amount held based on the RDD/IND threat and population at risk.

ASD (HA) acquired and will preposition stockpiles of Ca-DTPA and Zn-DTPA at Theater Lead Agents Medical Materiel (TLAMMs) in the Pacific rim, Europe, and south west Asia. ASD (HA) may authorize re-disposition of the stockpiles based on mission needs and risk assessments. DoD will not centrally stockpile Ca-DTPA or Zn-DTPA within the continental United States (CONUS).

RELEASE AUTHORITY

Materiel purchased by MTF is for use by that facility and its subordinate or supported units or facilities, specifically to respond to an RDD or IND. Authority to release this supply of Ca-DTPA and Zn-DTPA is vested in the MTF Commander, who retains operational control of these radiation countermeasures. Operational decisions regarding use of this supply will be consistent with the priorities for CA-DTPA and Zn-DTPA use presented in this policy, in addition to current clinical guidelines by cognizant public health specialists and organizations, and the FDA-approved product labels.

The stockpiles of Ca-DTPA and Zn-DTPA positioned by ASD (HA) outside the continental United States (OCONUS) remain within the control of ASD (HA); they are not released to the Services or Geographic Combatant Commanders (GCC). ASD (HA) will, as necessary, release all, or a portion of, the stockpile to the Joint Chiefs of Staff (JCS) should the risk to personnel become imminent or a radiological event (i.e., RDD or IND) occur. ASD (HA) will be advised on this decision by the Service Surgeons General, JCS, Commanders of Combatant Commands (CCDRs), the Joint Preventive Medicine Policy Group (JPMPG), and other advisory bodies.

For pre-event distribution, after ASD (HA) approval, the Defense Logistics Agency (DLA) will initiate shipments using standard medical logistics supply chain processes, or, if required, alternate GCC-directed means (e.g., military ground or air transport). For post-event distribution, DLA will initiate shipments using standard life-or-death medical logistics supply chain processes, or, if required, alternate GCC-directed means (e.g., military ground or air transport), as the products are most effective when administered immediately and up to the first 24 hours after internal contamination with the transuranic elements plutonium, americium, and curium. On a case-by-case basis, ASD (HA) will consider requests for JCS/CCDRs to create small stockpiles at other locations or in specific units, or authorize the release of portions of the stockpile.

Following ASD (HA) release of Ca-DTPA and Zn-DTPA, JCS, in coordination with U.S. Northern Command as the global synchronizer, and the affected CCDRs, will apportion these medications to GCCs for use OCONUS. Treatment with Ca-DTPA and/or Zn-DTPA should not begin until the Public Health Emergency Officer (PHEO) confirms release of an RDD or IND, or there is clinical diagnosis or suspected occurrence of internal contamination with the radioactive transuranic metals plutonium, americium, or curium.

GCCs should evaluate the threat of the release of the radioactive transuranics plutonium, americium, and curium and develop plans to protect personnel and to potentially receive, store, maintain, and rapidly distribute Ca-DTPA and Zn-DTPA to treat appropriately selected casualties. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after internal contamination when the radiocontaminant is still circulating and readily available for chelation.

INDICATIONS AND USAGE

Ca-DTPA and Zn-DTPA is FDA-approved for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. The manufacturer recommends Ca-DTPA for the initial treatment because Ca-DTPA results in about a 10-fold higher rate of elimination of plutonium in the urine as compared to Zn-DTPA when given during the first 24 hours after exposure. At 24 hours post exposure Ca- and Zn-DTPA are equally effective at the elimination of radioactivity.

Screen all potential casualties for their risk of internal contamination. Medically evaluate the resulting high-risk subpopulation. Presumptive casualties potentially requiring chelation treatment consist of two main groups. The first group includes individuals with a history of being near the RDD ground-zero or in the close (high zone) downwind plume footprint who present with findings of gross external radiocontamination on radiation detector screening of the upper body, especially contamination of the head, hair, and shoulders. The second potential high-risk group includes persons who were outdoors in the high exposure (high zone) areas but who escaped contamination screening at an exit point or triage site (unscreened). Screen persons presenting at the controlled exits of guided evacuation routes, or at triage points for potentially contaminated wounds or upper body contamination, and triage accordingly. Treatment is usually indicated when internal contamination exceeds ten times the Allowable Level of Intake (ALI). Treat the resulting known or suspected positives as soon as possible, pending diagnostic testing to determine their need for continuation of therapy.

OPERATIONAL EMPLOYMENT

Physicians, hospitals, and other DoD force health protection components will provide aid, to include the administration of Ca-DTPA and Zn-DTPA, to military personnel, their families, U.S. Government civilian workers, and U.S. Government contractors injured by a terrorist act involving radioactive material or a nuclear detonation. There are many scenarios for such acts that result in a range of exposures, and produce few to many casualties. Such events can take place in any environment.

RADIOLOGICAL MEDICAL SPECIALTY TEAMS

DoD has radiological medical specialty teams available to assist medical personnel in response to events of the type described in this policy (e.g., Armed Forces Radiobiology Research Institute (AFRRI) Medical Radiobiology Advisory Team, Service Radiological Advisory Medical Teams). The teams have various capabilities, including providing health physics, medical, and radiobiological advice to military and civilian command and control operations; evaluating radiation hazards; advising on contamination control, radiation exposure risks, and protective action guidelines; and providing radiological medical support. The teams are deployable and, through "reach back," can call on the knowledge and skills of radiobiologists, biodosimetrists, and other research professionals. Use of the teams' expertise in planning and response is strongly encouraged.

DOSAGE AND ADMINISTRATION

Chelation treatment is most effective within the first 24 hours after internal contamination. Start treatment as soon as possible after suspected or known internal contamination. Treat individuals who cannot receive immediate chelation treatment as soon as treatment capability becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination however, the chelating effects of Ca-DTPA / Zn-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 sequester in liver and bone.

It is preferable to administer Ca-DTPA, if available, as the initial dose during the first 24 hours after internal contamination because Ca-DTPA is more effective than Zn-DTPA during this time. When Ca-DTPA is contraindicated (e.g., pregnancy), Zn-DTPA may be used for the initial treatment. After 24 hours, Zn-DTPA and Ca-DTPA are equally effective. Additional therapies may be needed (e.g., Prussian blue, potassium iodide) if internal contamination with radiocontaminants other than plutonium, americium, or curium, or unknown radiocontaminants occurs.

Table 1 summarizes dosage and methods of administration of Ca-DTPA and Zn-DTPA; consult the individual product labels for definitive guidance (e.g., contraindications, precautions, dosage and administration).

After the initial dose, on the next day, if additional chelation therapy is indicated, it is preferable to switch to Zn-DTPA, if available, due to the safety concerns associated with prolonged Ca-DTPA use (e.g., calcium loss). If Zn-DTPA is not available, treatment may continue with Ca-DTPA, however mineral supplementation may be required. Evacuate patients requiring maintenance treatment to a medical treatment facility offering definitive care capability.

LABORATORY TESTS AND MONITORING

When possible, before initiating treatment, obtain baseline blood and urine samples, including Complete Blood Count (CBC) with differential, Blood Urea Nitrogen (BUN), serum chemistries and electrolytes, urinalysis, and blood and urine radioassays. To establish an elimination curve, a quantitative baseline estimate of the total internalized transuranic 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, monitor CBC with differential, BUN, serum chemistries and electrolytes and urinalysis regularly. If the individual is receiving more than one dose of Ca-DTPA, monitor these laboratory tests very carefully.

COLLECTION OF PATIENT TREATMENT DATA

Clinical staff will complete an AFRRI Adult / Pediatric Field Medical Record (Initial Contact Worksheet) and Biodosimetry Worksheet (Appendix I) for each patient treated to assist the health care provider in determining the duration of treatment. The worksheets are available from the Biodosimetry Tools section of the AFRRI web site (http://www.afrri.usuhs.mil/outreach/biodostools.htm#forms).

Clinical staff will complete the Ca-DTPA manufacturer Patient Treatment Form and/or the Zn-DTPA manufacturer Patient Treatment Form for each patient treated. The manufacturer requires the information to develop long-term response data and information on the risk of developing late malignancy. Mail completed forms to: Hameln Pharmaceuticals GMBH, Langes Feld 13, 31789 Hamlen, Germany. The forms are available from the U.S. commercial distributor's web site (http://www.akorn.com/dtpa_product_info.php).

LOGISTICS CONSIDERATIONS

Inventory Management: TLAMM and MTF storage locations shall track and account for any and all Ca-DTPA and Zn-DTPA inventory using existing Service and Joint medical logistics automated information systems (AIS) (e.g., Defense Medical Logistics Standard Support(DMLSS)). Inventory managers will ensure the on-hand balances and all quality assurance information is entered into their respective medical logistics AIS and that AIS is reporting the data to the Joint Medical Asset Repository (JMAR). JMAR will provide this data to the ASD (HA) Force Health Protection and Readiness Chemical, Biological, Radiological, and Nuclear (CBRN) Medical Dashboard.

Storage and Shipping Requirements: The temperature requirement for Ca-DTPA and Zn-DTPA, as defined on the product labels, is 15 - 30°C (59 - 86°F). Exposures outside the required storage temperatures could cause the product to lose efficacy, could lead to product adulteration that could threaten patient safety, and/or could lessen shelf life. Transport, store, and handle both products in accordance with the guidance provided on the product label and in the United States Pharmacopeia (USP), Chapter 1079, Good Storage and Transportation Standard. USP is the U.S. standard for the storage and handling of finished pharmaceutical products. Use controlled-temperature shipping containers validated for the season, mode, and transit time. Monitor temperatures during transport by placing electronic time and tracking temperature devices in every container, IAW local cold chain/thermal management standard operating procedures.

Security: Ensure the integrity of the medical logistics supply chain is secure. The risk to the product is that it will be diverted by those seeking monetary gain or by those who fear they will be not receive treatment (e.g., worried well, local nationals). The use of electronic track and trace technology (e.g., Radio Frequency Identification (RFID)) is encouraged.

Shelf Life/Expiration Dates: ASD (HA) acquired Ca-DTPA and Zn-DTPA each consist of a single lot, and so each has a single expiration date. The product has a 10-year shelf life from time of manufacture when stored and transported at the temperatures defined on the product labels. The lot numbers and expiration dates for ASD (HA) stockpiled materiel are in Table 2.

Shelf Life Extension: Ca-DTPA and Zn-DTPA are not entered in the DoD/FDA Shelf Life Extension Program (SLEP). ASD (HA) is exploring SLEP eligibility for both products and will provide guidance at a future date.

Associated Supplies: The majority of the supplies needed are commonly present in existing medical treatment facilities (e.g., needles, syringes, intravenous sets). If TLAMMs or MTFs push Ca-DTPA and/or Zn-DTPA to a treatment team or smaller

MTF, or if treatment is conducted outside a medical treatment facility (e.g., gymnasium, tent), do not assume that all required supplies are, or will, be available. MTF commanders and TLAMMs will coordinate with the supported medical treatment facilities / medical response teams to determine the identity and quantity of associated supplies necessary to initiate and sustain treatment with Ca-DTPA and Zn-DTPA, will develop support kits as required, and will ensure the support kits and Ca-DTPA/Zn-DTPA are delivered simultaneously.

RESUPPLY AND REPLENISHMENT

Resupply during a contingency (e.g., response to release of an RDD or IND): CONUS MTFs shall coordinate for resupply with local, territorial, and state Strategic National Stockpile Coordinators. OCONUS MTFs shall requisition materiel from their supporting TLAMM. National Stock Numbers and National Drug Codes for each product are in Table 2; additional logistics data is in Tables 3 and 4.

Replenishment of MTF-Acquired Materiel: Replenishment of MTF-acquired materiel is the responsibility of the Services / MTFs. TLAMMs shall not use the ASD (HA) acquired stockpile materiel to replenish MTFs.

Replenishment of ASD (HA)-Acquired Ca-DTPA and Zn-DTPA Stockpile: ASD (HA) acquired Ca-DTPA and Zn-DTPA to ensure immediate access in the event of RDD or IND release. Replenishment of the DoD stockpile is the responsibility of the GCCs, Services, and DLA.

Table 1: Dosage and Administration of Ca-DTPA and Zn-DTPA for the Treatment of Internal Contamination With the Radioactive Transuranic Elements Plutonium, Americium, & Curium

SEE NOTES 1 and 2		Ca-DTPA	Zn-DTPA
INITIAL DOSE	**ADULT**	Single 1.0 gram (i.e., 1000 milligrams, one ampoule), once a day	• Unless contraindicated (e.g., pregnancy) it is preferable to administer CA-DTPA as the initial dose during the first 24 hours after internal contamination. • If indicated, administer single 1.0 gram (i.e., 1000 milligrams (mg), one ampoule), once a day
	PEDIATRIC	Single dose of 14 mg/kilogram (kg), one a day, not to exceed 1.0 gram	• It is preferable to administer CA-DTPA as the initial dose during the first 24 hours after internal contamination. • Single dose of 14 mg/kg, once a day, not to exceed 1.0 gram
MAINTENANCE DOSE	**ADULT**	• After the initial dose, on the next day, if additional therapy is indicated, it is preferable to switch to Zn-DTPA, if available. • If Zn-DTPA is not available, treatment may continue with Ca-DTPA, but mineral supplements should be given concomitantly, as appropriate • Single 1.0 gram (i.e., 1000 mg, one ampoule), once a day	• After the initial dose, on the next day • Single 1.0 gram (i.e., 1000 mg; one ampoule), once a day
	PEDIATRIC	• After the initial dose, on the next day, id additional therapy is indicated, it is preferable to switch to Zn-DTPA, if available. • If Zn-DTPA is not available, treatment may continue with Ca-DTPA, but mineral supplements should be given concomitantly, as appropriate • Single dose of 14 mg/kg, once a day, not to exceed 1.0 gram	• After the initial dose, on the next day • Single dose of 14 mg/kg, once a day, not to exceed 1.0 gram
METHOD OF ADMINISTRATION	**INTRAVENOUS (IV)**	• IV administration s recommended and should be used if route of internal contamination is not known or multiple routes of internal contamination are likely • Administer solution (1 gram in 5 milliliters (mL)) with either a slow IV push over a period of 3-4 minutes or by intravenous infusion over 30 minutes, diluted in 100-250 mL of 5% dextrose in water (D5W), Ringers Lactate, or normal saline	
	NEBULIZATION	Where internal contamination is only by inhalation within the preceding 24 hours	Where internal contamination is only by inhalation
		• Dilute at a 1:1 ratio with sterile water or saline • The safety and effectiveness of the nebulized route has not been established in the pediatric population	

NOTES:

1. Do not administer Ca-DTPA and Zn-DTPA via the intramuscular route.
2. Chelation is most effective if administered within the first 24 hours after internal contamination and should be started as soon as possible after suspected or known internal contamination.

Table 2: Product Identification, Lot Numbers, & Expiration Dates for ASD (HA) Acquired Ca-DTPA and Zn-DTPA Stockpile

Product	Description	National Stock Number (NSN)	National Drug Code (NDC)	Lot Number	Expiration Date
Ca-DTPA	200 mg/mL single use ampoules	6505-01-526-6210	52919-001-03	641060	31-Oct-16
Zn-DTPA	200 mg/mL single use ampoules	6505-01-526-6547	52919-002-03	R446060	30-Nov-14

Table 3: Pentetate Calcium Trisodium Injection (Ca-DTPA) & Pentetate Zine Trisodium Injection (Zn- DTPA) Logistics Data

Description	Size of Ampoule	Ampoule Strength	Unit of Sale	Intermediate Package	Case
200 mg/mL single use glass ampoules (amps)	5 mL	1000 mg (1 gram)	Box of 10 amps	10 Boxes Shrink-wrapped (1 Bundle (Bndl))	10 Bndls

Table 4: Manufacturer, Distributor, Case Weight & Dimensions of Ca-DTPA and Zn-DTPA

Manufacturer	Distributor	Case Dimension	Case Wt
Hameln Pharmaceuticals	Akom	515 millimeter (mm) high x 380 mm wide x 207 mm deep (8.15" x 20.28" x 14.96")	13 kg (28.7 pounds)