

Evaluation and Research's (CDER's) Division of Medical Imaging and Radiopharmaceutical Drug Products for a copy of the draft labeling (see **ADDRESSES**). We also recommend that you consult the guidance entitled "Calcium-DTPA and Zinc-DTPA Drug Products—Submitting a New Drug Application," which is being made available with this notice (see section V of this document).

#### *A. Basis for Finding of Safety and Effectiveness*

We have reviewed medical reports in the REAC/TS database and have determined that Ca-DTPA and Zn-DTPA drug products, when produced under conditions specified in an approved NDA, 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. Our conclusion is supported by our review of reports in the literature, which provided information consistent with that in the REAC/TS database.

Administration of a loading dose of Ca-DTPA followed by maintenance treatment with Zn-DTPA increases the rate of elimination of these radioactive elements from the body and is expected to decrease the risk of death and major morbidity from radiation complications.

In reaching our determination on the effectiveness of Ca-DTPA and Zn-DTPA, we evaluated reports from the REAC/TS database on 646 patients who received one or more doses of these drugs during the last 40 years. Ca-DTPA was administered either by inhalation or by intravenous injection. Zn-DTPA was administered by intravenous injection. Data on the type of transuranium element and amount of urine elimination were available for detailed analysis from 18 patients. In these patients, administration of Ca-DTPA by inhalation or intravenous injection of a 1-gram (g) dose of Ca-DTPA in a 5 milliliter (mL)-sterile aqueous solution increased the rate of radiation elimination in the urine an average of 39-fold. Maintenance doses of Zn-DTPA administered once daily resulted in continued elimination of radiation.

Some adverse effects were identified as resulting from Ca-DTPA and Zn-DTPA administration. The primary adverse effects of Ca-DTPA administration were the elimination from the body of endogenous essential trace metals, particularly zinc, but also including magnesium and manganese. The endogenous trace metal decreases occurred after treatment for several days and appeared to increase when the

drugs were given in divided doses over 1 day. Although Zn-DTPA is also believed to decrease serum magnesium and manganese, no serious toxicity has been observed with the administration of Zn-DTPA in humans or animals. In patients undergoing administration of Ca-DTPA or Zn-DTPA drug products, blood levels of these endogenous trace metals should be followed closely and can be treated with nutritional supplements.

In pregnant animals, multiple doses of Ca-DTPA are associated with fetal malformations and fetal death. Similar effects on animal fetuses were not seen with Zn-DTPA. As a result, Zn-DTPA should be used to begin treatment in pregnant patients. However, if Zn-DTPA is not available, the risks related to radiation contamination should be weighed against the risks of Ca-DTPA to the mother and fetus.

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. In patients whose contamination is only by inhalation within the preceding 24 hours, Ca-DTPA administered as a single loading dose by nebulized inhalation is an alternative route of administration. However, administration of Ca-DTPA by inhalation may irritate some patients, especially those with a history of respiratory disorders. In these patients, the intravenous route can be used. Other rare adverse events are discussed in the published literature and in the draft labeling we have prepared.

#### *B. Labeling for Ca-DTPA and Zn-DTPA*

We have prepared draft labeling for Ca-DTPA supplied as 1 g in a 5 mL-sterile aqueous solution for administration either by inhalation (with a 1:1 dilution with saline and delivered by nebulization) or intravenous injection. We have also prepared draft labeling for Zn-DTPA supplied as 1 g in a 5-mL sterile aqueous solution for intravenous injection. You can submit this draft labeling as part of an NDA for Ca-DTPA or Zn-DTPA drug product that relies on our findings of safety and effectiveness. The draft labeling reflects our conclusion on the potential safety and effectiveness of Ca-DTPA and Zn-DTPA 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 NDA, additional literature or other studies to support your requested changes. If you submit an NDA for either a Ca-DTPA or Zn-DTPA drug product that is not based on our findings of the safety and effectiveness of Ca-DTPA and Zn-DTPA, you cannot use the draft labeling because it is based on our review of the REAC/TS database and published literature. If you submit such an NDA, your labeling must be based on the safety and effectiveness data contained in your NDA.

The draft labeling for NDAs based on our review of the REAC/TS database and published literature is available on the Internet at <http://www.fda.gov/cder/drug/infopage/dtpa/default.htm>. You may also contact CDER's Division of Medical Imaging and Radiopharmaceutical Drug Products for a copy of the draft labeling (see **ADDRESSES**).

### **III. Conclusions**

We have determined that Ca-DTPA and Zn-DTPA can 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. We encourage the submission of NDAs for Ca-DTPA and Zn-DTPA drug products. The requirement under 21 U.S.C. 355(b)(1) for full reports of investigations to support these NDAs may be met by citing this notice and the published literature we relied on in preparing this notice. For a list of this published literature see section V of this document. A list of the published literature and reprints of the reports will be available for public inspection in the Division of Dockets Management (see **ADDRESSES**). It is unnecessary to submit copies and reprints of the reports from the listed published literature. We invite applicants to submit any other pertinent studies and literature of which they are aware.

### **IV. Availability of a Guidance**

#### *A. Notice of Availability*

In this document, we are also announcing the availability of a guidance for industry entitled "Ca-DTPA and Zn-DTPA Drug Products—Submitting a New Drug Application." The guidance is intended to assist manufacturers who plan to submit NDAs for Ca-DTPA and Zn-DTPA.