November 26, 2010

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to 21 CFR 10.25(a), 10.30 and in accordance with 314.122 and 314.161(a)(3) requesting the Commissioner of the Food and Drug Administration to make a determination as to whether the drug product covered by NDA 21-749 (Pentetate Calcium Trisodium, Hameln Pharms) that has been voluntarily withdrawn from sale in the United States was withdrawn for safety or effectiveness reasons.

We refer to our abbreviated new drug application (ANDA) dated April 27, 2010, submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Pentetate Calcium Trisodium Injection, 200 mg/mL, 5 mL vials.
A. Action Requested

The petitioner is seeking a determination by the Commissioner that Hameln Pharms' voluntary withdrawal of Pentetate Calcium Trisodium from sale was for reasons other than safety or effectiveness.

B. Statement of Grounds

The listed drug and basis of our ANDA, subject of NDA 21-749, held by Hameln Pharms., has been moved into the "Discontinued Section" of the Orange Book. According to section 1.11 of the Preface to the Orange Book; a drug product in the Discontinued Section as to which a determination has already been made that withdrawal was not for safety and effectiveness reasons will have the following statement after its product strength: "Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons." There is no such annotation next to the product strength for Pentetate Calcium Trisodium. Attachment I.

Ditripentat-Heyl® (DTPA) (=Ca-DTPA) and Zink-Trinatrium-pentetat (Zn-DTPA) have been marketed in Germany for decades. More than 40 years of therapeutic use and experience have shown the suitability of the formulations. No reports of side effects have been submitted to HEYL as marketing authorization holder during these years. The DTPA products however are also available to other countries, where they can be distributed in accordance with special regulations on an emergency basis in case of contamination with transuranic radioactive isotopes. For example physicians from NIRS in Japan are authorized to use these products. They have been supplied to the following countries: Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Hong Kong, India, Italy, Japan, Korea, Malaysia, Netherlands, Pakistan, Switzerland, Spain, and Taiwan. No reports about side effects or ineffectiveness were submitted to Heyl.
Traditional clinical trials have not been conducted because it would be unethical to deliberately expose patients to radiation or toxic compounds; on the other hand it would also be unethical to withhold potential beneficial medications from patients who have been accidentally exposed. Therefore accidentally exposed patients were treated empirically and the findings were reported in the literature as observational studies. HEYL has established a monitoring of the scientific literature and notices of Health authorisations:

- Subscription to FDA MedWatch
- Periodical searches in medical databases (MEDLINE, Excerpta Medica, Biosis, REAC)
- Monitoring of the world-wide-web by appropriate GOOGLE Alerts.

No reports about negative benefit risk estimation were found.

Ca-DTPA and Zn-DTPA are still recommended by different organizations, for example:


The FDA has reviewed the published literature available up to the year 2003 and summarized the data on the effectiveness and safety of Ca-DTPA and Zn-DTPA in 2003. In addition the FDA has used data from the REAC/TS DTPA Registry database. REAC/TS coordinated the national use of Ca-DTPA and Zn-DTPA for decorporation therapy in the USA for several decades (IND 4,041 Ca-DTPA and IND 14,603 Zn-DTPA) and distributed the drug products to all DTPA co-investigators. The distribution has been approved by both the US FDA and DOE. 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.
The results are published in the "Guidance for Industry on Pentetate Calcium Trisodium and Pentetate Zinc Trisodium for Treatment of Internal Contamination with Plutonium, Americium, or Curium; Availability" [Federal Register, Vol. 68, No. 178/Monday, September 15, 2003]. In this document the FDA concluded, that Ca-DTPA and Zn-DTPA drug products, when produced under conditions specified in approved NDAs, can be found to be safe and effective for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase their rates of elimination. "No serious toxicity in human subjects has been reported as a result of 625 separate patients administered DTPA (either intravenously by slow i.v. push or by nebulizer) in recommended doses (for a total of 4,565 separate doses). In addition, no serious adverse effects have been noted as a result of over 1,000 doses of Zn-DTPA in the recommended dosage given to a single individual." Attachment II.

The findings of the FDA are also valid for Ditripentat-Heyl® (DTPA) and Zink-Trinatrium-pentetat (Zn-DTPA) because the drug products used by REAC/TS had been manufactured by Heyl.

The new data published between 2003 and 2010 are suitable to confirm the conclusion of the FDA. In particular experiences from France [Attachments III, IV] and Germany [Attachment V] demonstrate the benefit of the clinical use of Ca-DTPA or Zn-DTPA:

In the CEA and AREVA plants in France 1,158 injections, which had been administered to 469 persons because of possible or confirmed contaminations, were reported from 1970 to 2003.
- 332 patients received 1 single injection of Ca-DTPA;
- 46 patients received a single injection several times per distinct event;
- 68 patients received 2, 3 or 4 injections after the same event;
- 23 patients received 5 or more injections after the same event. The number of injections for this group is 518. One patient was treated with 245 injections over 4 years.
The urinary excretion of the actinides is significantly increased by the factor 25 to 100 as
compared to the spontaneous excretion. Among the 1,158 injections applied to 469
patients, only one undesirable effect was recorded (immediate allergic cutaneous
reaction). Attachments III, IV.

From 1971 until 2003, a total of 50 persons were treated with 190 DTPA doses in the
Forschungszentrum Karlsruhe in Germany. As detailed data on the back then new therapy
were lacking, the treatments varied: 0.5 g, 1 g or 2 g, Zn-DTPA or Ca-DTPA, in form of
infusions, i.v. injections or aerosols. Administration of 2 g DTPA did not result in increased
excretion compared to the administration of 1 g DTPA, whereas application of 0.5 g DTPA
led to a smaller excretion rate. Zn-DTPA was applied 106 times and Ca-DTPA 84 times. 5
(10 ml or 1 g) aerosol applications, 17 injections, and 168 infusions were made. From
January 1986 onwards, DTPA was applied via infusions only. Long-term therapies were
carried out with Zn-DTPA, as it has the same effect, but is less toxic than Ca-DTPA. One
patient who was administered Ca-DTPA once-daily noted weakness after the second
application. According to the records there were no other incidents reported on the
treatments with DTPA. Attachment V.

In the Mayak Worker Study Project in Russia the records of 1,179 workers were
obtained. Some of these workers received chelate therapy more than once, resulting in
1237 analysed cases. The majority of these workers had been exposed to plutonium prior to
1961. The typical protocol was that Ca-DTPA was injected intravenously with a dose of 0.25

Six workers contaminated with americium were treated in the Czech Republic with
Ca-DTPA. Examinations of the urine proved the increased excretion of the radionuclide. The
treatment was well tolerated, no adverse effects were observed. Attachment VIII.
Three workers were treated with Ca- and/or Zn-DTPA after exposition to $^{241}$Am. Up to 10 doses were applied. DTPA proved effective to enhance urine excretion of $^{241}$Am. There were no significant adverse clinical health effects of the therapy. Attachment IX.

Chelation treatments with dosages of 1 g of either Ca-DTPA or Zn-DTPA were undertaken at Los Alamos Occupational Medicine in three cases of wounds contaminated with metallic forms of Pu. One subject was treated only once, while the other two received multiple injections. There is no note on side effects of the treatment. Attachment X.

The WHO/ International Programme on Chemical Safety (IPCS) recommends the following use of DTPA [Attachment XI]: "Pentetic acid salts should be used in cases of inhalation, dermal or wound exposure to americium, californium, cerium, curium and plutonium. It can also be considered for other transuranics and radioactive metals or metals where data are limited or unavailable or where other chelators are unavailable or ineffective. This includes cobalt, einsteinium, iron, lanthanum, nickel, promethium, scandium, strontium, ytterbium, yttrium and zinc."

As stated in the literature about the risk of DTPA, "Pentetic acid salts are generally well tolerated and repeated dosing may be needed for years after exposure to a radioactive element. There were no adverse effects reported in a worker exposed to americium given 583 g of pentetic acid salts over a 5 year period (Breitenstein & Palmer, 1989). In another case no adverse effects were reported after 322 g over 337 weeks with the longest period of uninterrupted treatment of 1 g/week for 134 weeks (Rosen et al., 1980)." "Adverse effects reported include nausea, diarrhoea, headache, light-headedness, chest pain, allergic reactions, dermatitis, microhaematuria, metallic taste and injection site reactions. Cough and/or wheezing may occur after nebulised calcium trisodium pentetate; patients with preexisting asthma may be more at risk. Calcium trisodium pentetate also chelates trace elements and these should be monitored in patients receiving repeated or long-term dosing with calcium trisodium pentetate. Supplements should be given as required."
In consideration of all available data with respect to the benefit risk estimation and the current scientific level of knowledge the application of Ca-DTPA and Zn-DTPA can be regarded as effective and safe. There are no medical findings which are opposed to an approval of the drugs.

We conclude, on the basis of the research outlined above, that discontinuation of Pentetate Calcium Trisodium was undertaken voluntarily and for reasons other than safety or effectiveness. We request that, if the Commissioner confirms our conclusion, the agency annotate the listing for Pentetate Calcium Trisodium in the Orange Book to indicate that it was not withdrawn for reasons of safety or effectiveness. If instead the Commissioner determines that Pentetate Calcium Trisodium was withdrawn from sale for safety or effectiveness reasons, we request that the agency publish a notice of this determination in the Federal Register.

The petitioner respectfully requests that the Commissioner take the requested action as soon as possible.

C. Environmental Impact Statement

A claim for categorical exclusion from the requirement of submission of an environmental assessment is made pursuant to 21 CFR § 23.31.

D. Economic Impact Statement

In accordance with 21 CFR § 10.30 (b), economic impact information will not be submitted unless requested by the Commissioner.
E. Certification

The undersigned certifies that, to the best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavourable to the petition.

Respectfully submitted,

Heyl Chem.-pharm. Fabrik GmbH & Co. KG

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Attachments