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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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Certifier A. Corbin

[Docket No. 03D–0023]

Guidance for Industry on Prussian Blue for Treatment of Internal Contamination With Thallium or Radioactive Cesium; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that we have concluded that prussian blue, when produced under conditions specified in approved new drug applications (NDAs), can be found to be safe and effective for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. We encourage the submission of NDAs for prussian blue drug products. We are also announcing the availability of a guidance for industry entitled "Prussian Blue Drug Products—Submitting a New Drug Application." This guidance is intended to assist manufacturers who plan to submit NDAs for prussian blue.

DATES: Submit written or electronic comments on agency guidances at any time.

ADDRESSES: Submit NDAs to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852. Submit requests for copies of draft labeling to the Division of Medical Imaging and Radiopharmaceutical Drug Products, (HFD–160), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7510. Copies of the reports

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referred to in this document will be on display at the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written requests for single copies of the guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Dockets Management Branch (address provided in third sentence of this paragraph). Submit electronic comments to http://www.fda.gov/dockets/ecomments. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Kyong Kang, Center for Drug Evaluation and Research (HFD–160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7510.

SUPPLEMENTARY INFORMATION:

I. Background

A. Cesium

Cesium-137, a radioactive isotope of cesium, was discovered in 1941 by Glenn T. Seaborg and Margaret Melhase. Cesium-137 is a product of fusion and is found in the fallout from the detonation of nuclear weapons and the waste from nuclear power plants. Cesium-137 is one of the most common radioisotopes used in industry. It is used in various measuring devices, such as moisture-density gauges. Cesium-137 is also widely used as a source of gamma radiation for treatment of various forms of cancer. Cesium-137 has a half-life of 30.07 years.

Contamination with cesium-137 can cause serious illness or death, depending upon the dose, and has been associated with the development of cancer long after exposure. In addition to concerns about exposure to cesium–137 in industrial and medical environments, cesium-137 contamination is of particular concern because it has been mentioned as a potential component of a radiological dispersal device (RDD), commonly called a "dirty bomb." An RDD is a conventional explosive or bomb containing radioactive material. The conventional bomb is used as a means to spread radioactive material, such as cesium-137. An RDD is not a nuclear bomb and does not involve a nuclear explosion.

B. Thallium

Thallium occurs naturally in several minerals and ores. It was discovered independently by both William Crookes and Claude Auguste Lamy in the early 1860s. Thallium is very toxic, and thallium sulfate has been used as a rat and ant poison in the past. Other thallium compounds are used in the manufacture of semiconductors, photocells, optical glass, and other items. Thallium-201, a radioactive isotope of thallium, is widely used in very small doses as an approved radioimaging drug. Thallium-201 has a half-life of 72.912 hours.

Acute exposure to high dose radioactive or nonradioactive thallium is generally characterized by severe gastrointestinal symptoms followed by neurological symptoms, which may lead to death. The toxicity resulting from chronic exposure to thallium is characterized by various neurological symptoms. Thallium-201 has also been mentioned as a potential component of a dirty bomb.

There are no approved treatments for internal contamination with thallium or radioactive cesium.

C. Prussian Blue

Prussian blue was first synthesized in 1704 by a Berlin color maker named Diesbach. It has been used as an industrial and artists' pigment ever since. The chemical name for prussian blue is ferric hexacyanoferrate(II).

Since the 1960s, prussian blue has been used investigationally as an orally ingested drug to enhance the excretion of isotopes of cesium and thallium from the body by means of ion exchange. However, there is currently no approved NDA for prussian blue. Prussian blue has a very high affinity for cesium and thallium. Cesium and thallium ions are ordinarily excreted into the intestine, reabsorbed from there into the bile, and then excreted again into the gastrointestinal tract. Orally administered prussian blue traps thallium or cesium in the intestine, interrupts its reabsorption from the gastrointestinal tract, and thereby increases fecal excretion of thallium and cesium. Prussian blue itself is not absorbed across the intestinal wall in significant amounts.

Prussian blue, in 500-milligram (mg) capsules, has been distributed by the Radiation Emergency Assistance Center/Training Site (REAC/TS) under investigational new drug application (IND) number 51,700. 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. ORISE owns the IND for prussian blue. The 500-mg capsules used under the IND are manufactured by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG (HEYL). HEYL uses the trade name Radiogardase-Cs for its 500-mg capsules of prussian blue.

II. Safety and Effectiveness of Prussian Blue Drug Products

We have concluded that prussian blue, when produced under conditions specified in approved NDAs, can be found to be safe and effective for the

treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. As described in the following paragraphs, our conclusion is based upon our review of published information.

We encourage the submission of NDAs for prussian blue drug products. If you are interested in submitting an NDA for this product, please contact us. We also recommend that you consult the guidance "Prussian Blue Drug Products—Submitting a New Drug Application," which is being made available with this notice.

A. Basis for Finding of Safety and Effectiveness

We have reviewed the published literature and have determined that 500–mg prussian blue capsules, when produced under conditions specified in an approved NDA, can be found to be safe and effective for the treatment of patients with known or suspected internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. Prussian blue increases the rate of elimination of thallium or radioactive cesium. Administration of prussian blue decreases the risk of death and major morbidity after exposure to radioactive thallium, nonradioactive thallium, or radioactive cesium.

In reaching our determination on the effectiveness of prussian blue, we evaluated published reports of a 1987 incident in Goiânia, Brazil, where approximately 250 people were contaminated with cesium-137 that had been abandoned after use in a cancer clinic (see International Atomic Energy Agency, 1998). Forty-six patients with heavy internal contamination were treated with prussian blue. Data on the whole-body effective half-life of cesium-137 during treatment and after treatment with prussian blue was completed on 33 of the 46 patients. The untreated mean whole-body effective

half-life of cesium-137 is 80 days in adults, 62 days in adolescents, and 42 days in children. Prussian blue reduced the mean whole-body effective half-life of cesium-137 by 69 per cent in adults, by 46 per cent in adolescents, and by 43 per cent in children (see International Atomic Energy Agency, 1998). Data from additional literature articles, including a study of 7 human volunteers contaminated with trace doses of cesium-137 and reports on 19 patients contaminated with cesium-137 in other incidents, show a similar reduction in whole-body effective half-life after administration of prussian blue (see Madhus, 1968 and National Council on Radiation Protection and Measurement, 1979).

We also evaluated reports in the literature that describe 33 patients who were treated with prussian blue for nonradioactive thallium poisoning. Prussian blue treatment reduced the mean serum biologic half-life of thallium from 8 days to 3 days (see Barbier, 1974; De Groot, 1985; Van Kesteren, 1980; and Vrij, 1995).

The primary adverse effects of prussian blue are constipation and nonspecific gastrointestinal distress. These side effects are more troublesome at high doses and respond to treatment with orally administered fiber (see Farina, 1991). Other rare adverse events are discussed in the published literature and in the draft labeling we have prepared.

B. Labeling for Prussian Blue

We have prepared draft labeling for orally administered drug products containing 500-mg prussian blue capsules. You can submit this draft labeling as part of an application for 500-mg prussian blue capsules that relies on our findings of safety and effectiveness. The draft labeling reflects our conclusion on the potential safety and effectiveness of 500-mg prussian blue drug products

for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. If you wish to change the labeling to include a different or broader indication, different dosage, or make any other significant changes to the draft labeling, you should provide, as part of your application, additional literature or other studies to support your requested changes. If you submit an application for a prussian blue drug product that is not based on FDA's findings of safety and effectiveness of prussian blue, you may not use the draft labeling because it is based on our review of the published literature. If you submit such an application, your labeling must be based on the safety and effectiveness data contained in your NDA.

The draft labeling for applications based on this finding of safety and effectiveness is available on the Internet at http://www.fda.gov/cder/foi/label/2003/ind51700lbl.pdf. You may also contact the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products for a copy of the draft labeling (see **ADDRESSES**).

III. Conclusions

We have determined that 500-mg prussian blue capsules can be safe and effective for the treatment of patients with known or suspected internal contamination with radioactive thallium, nonradioactive thallium, or radioactive cesium. We encourage the submission of NDAs for prussian blue 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 the published literature we relied on in preparing this notice. A list of the published literature and reprints of the reports will be available for public inspection in the Dockets Management Branch (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 notice, we are also announcing the availability of a guidance for industry entitled, "Prussian Blue Drug Products—Submitting a New Drug Application." The guidance is intended to assist manufacturers who plan to submit NDAs for prussian blue.

This guidance is being issued as a level 1 guidance consistent with FDA's good guidance practices regulation (21 CFR 10.115). It is being implemented immediately without prior public comment because the agency believes it is in the interest of the public health to communicate this information to the public as quickly as possible. However, the agency welcomes comments on the guidance and, if comments are submitted, the agency will review them and revise the guidance if appropriate. The guidance represents the agency's current thinking on issues associated with the submission of NDAs for prussian blue. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

B. Comments

Interested persons may, at any time, submit written or electronic comments on the guidance to the Dockets Management Branch (see **ADDRESSSES**). Two copies of any mailed comments are to be submitted except that individuals may submit one copy. Comments are to be identified with

the docket number found in the brackets in the heading of this document. The document and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

C. Electronic Access

Persons with access to the Internet may obtain the guidance at either http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/ohrms/dockets/default.htm.

V. Published Literature on the Safety and Effectiveness of Prussion Blue

The published literature we have relied on in making the determinations regarding prussian blue contained in this notice is listed in this section of this document. Copies of the published literature will be on display in the Dockets Management Branch (see **ADDRESSES**) and can be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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15. International Atomic Energy Agency, *Dosimetric and Medical Aspects of the Radiological Accident in Goiania in 1987*, Vienna, IAEA–TECDOC–1009, 1998.

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18. Kargacin, B. et al., "The Influence of a Composite Treatment for Internal Contamination by Several Radionuclides on Certain Health Parameters in Rats," *Arhiv za Higijenu Rada i Toksikologiju*, 36:165–172, 1985.

19. Kostial, K. et al., "Simultaneous Reduction of Radioactive Strontium, Caesium, and Iodine Retention by Single Treatment in Rats," *The Science of the Total Environment*, 22:1–10, 1981.

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21. Kostial, K., B. Kargacin, and I. Simonovic, "Efficacy of a Composite Treatment for Mixed Fission Products in Rats," *Journal of Applied Toxicology*, 3:291–296, 1983.

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38. Richmond, C. R., and D. E. Bunde, "Enhancement of Cesium–137 Excretion by Rats Maintained Chronically on Ferric Ferrocyanide," *Proceedings of the Society for Experimental Biology and Medicine*, 121:664–670, 1966.

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Dated: 1/28/03
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Margaret M. Dotzel,
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