Radiogardase®
(Prussian blue insoluble capsules)

Radioactive Cesium-137:

Are you prepared?
Radioactive Cesium-137 can be found in hospitals, factories, construction sites, and food processing plants. Radiological materials also are available on the international black market, and according to the International Atomic Energy Agency, Cesium-137 has been the second most frequently intercepted radiological material in recent years. Cesium-137 would be particularly useful as a weapon of terror, for example, as the radioactive element in a “dirty bomb.”

Patients can become internally contaminated with Cesium-137 particles by swallowing them, inhaling them, or absorbing them into the bloodstream through wounds or the skin. High levels of internal Cesium-137 contamination can cause serious illness or death when contamination results in the absorption of high levels of radiation by critical organs. Lower levels of exposure have been associated with the development of cancers. The only effective method of reducing these risks is removal of the Cesium-137 from the body, and the sooner treatment begins after internal contamination is known or suspected, the better for patient outcomes.

**Counteraction**

Only one pharmaceutical countermeasure - Radiogardase® (Prussian blue insoluble capsules) - has been approved by the U.S. Food and Drug Administration as safe and effective for treating patients over the age of two years known or suspected to be internally contaminated with Cesium-137, radioactive Thallium-201, and non-radioactive Thallium to increase their rates of elimination from the body. Radiogardase® is not absorbed through the wall of the stomach and intestinal tract. It is not metabolized like other drugs. Instead, Radiogardase® works by binding to radioactive Cesium-137 particles present in the digestive tract, reducing the number of particles from being recirculated in the body and allowing them to be more rapidly eliminated from the body through the digestive tract. Radiogardase® has been shown to reduce the whole-body effective half-life of Cesium-137 by 69 percent in adults, 46 percent in adolescents, and 43 percent in children.

**Limitations on Use**

While Prussian blue increases the rate of elimination of radioactive Cesium-137 and Thallium-201 from the body, it does not treat complications of radiation toxicity, such as bone marrow suppression, neutropenia, or thrombocytopenia. Patients suspected of being internally contaminated with Cesium-137 should be monitored for radiation toxicity and treated as necessary. Prussian blue might not increase the rates of elimination from the body of radioactive elements other than Cesium-137 and patients exposed to radioactive elements in addition to Cesium-137 may require additional, concomitant treatment with other agents.

**Side Effects**

There have been no reports of deaths or serious or severe adverse events attributed to the use of Prussian blue. Known side effects include constipation (24%), and undefined gastric distress. Constipation was successfully treated with a high fiber diet. A blue discoloration of the mouth and teeth might occur when powder from Prussian blue capsules is mixed with food for administration to patients unable to swallow capsules. Prussian blue might bind to electrolytes or other therapeutic drugs in the gastrointestinal tract. Serum electrolyte levels should be monitored during treatment, particularly in patients with pre-existing cardiac arrhythmias or electrolyte imbalances, as should possible clinical responses to critical orally administered drugs. Prussian blue’s potential effects on pregnancies have not been studied.

**First-Aid for First Responders**

Patients suspected of being internally contaminated with Cesium-137 should be treated with Radiogardase® as soon as possible after contamination is suspected and contamination should be verified through medical examination as soon as possible thereafter. If available, Radiogardase® could be administered to rescue workers responding to suspected Cesium-137 events before they arrive on the scene. The anticipatory or immediate administration of Radiogardase® will not prevent first responders from becoming internally contaminated, but will ensure that the drug will be available to start working immediately if they become internally contaminated with Cesium-137. Dosage for first responders should be three grams (six capsules) three times per day for a minimum of thirty days.

**The Security of Treatment**

Please see the approved package insert at the end of this brochure for additional details regarding Radiogardase®.
The results of fecal analysis from those patients contaminated with
% Injected
1.17 (1.64 – 0.84) 10
14
7 3
6
80
4 - 9
27
Prussian blue insoluble showed higher activities of

Animal Data: Dose-response studies have not been conducted in human subjects. In a study using rats (n = 40, other elements (e.g., potassium), and cause electrolyte or other nutritional imbalances. (See PRECAUTIONS, tissue, has a biological half-life of 8 – 10 days. Thallium also follows the movement of potassium and is excreted

molecular weight of 859.3 Daltons. It is provided as 0.5 gram of Prussian blue powder in
cubic lattice with the FeII and FeIII atoms occupying the corners of the
cube and the cyanide groups positioned on the sides.

The crystal structure of Prussian blue is a

The rate of Cesium and Thallium elimination was proportional to the duration and dose of Prussian blue insoluble. (See CLINICAL PHARMACOLOGY, Pharmacokinetics) A radioactive element has a constant rate of disintegration that is reflected by its biological half-life. The combined rate of radiation disintegration and rate of element elimination is reflected by the effective half-life. Cesium-137 (137Cs) has a physical half-life of 30 years with a beta energy peak at 174.9 keV. Following entry into the blood, it is distributed uniformly through all body tissues. Approximately 10% of Cesium is eliminated rapidly with a biological half-life of 2 days, and 90% is eliminated more slowly, with a biological half-life of 110 days. Less than 1% of the Cesium was retained with a longer biological half-life of about 500 days. Cesium follows the movement of potassium and is excreted into the intestine, reabsorbed from the gut into the blood, then to the bile, where it is excreted again into the gut (enterohepatic circulation).

Without Prussian blue insoluble treatment, ~80% of Cesium is excreted through the kidneys and ~20% in the feces. Because of Cesium’s long physical half-life, the rate of radiation elimination is similar to the rate of element elimination from the body. Thallium-201 (201Tl) has a physical half-life of 8 – 10 days. Thallium also follows the movement of potassium and is excreted by the bile in enterohepatic recirculation. Without Prussian blue insoluble treatment, the fecal tourine excretion ratio of Thallium is approximately 2:1. Based on the mechanisms of action, Prussian blue insoluble may bind other elements (e.g., potassium), and cause electrolyte or other nutritional imbalances. (See PRECAUTIONS, Laboratory Tests.)

Dose-Response Relationship
Animal Data: Dose-response studies have not been conducted in human subjects. In a study using rats (n = 40), mean body weight range of 188 – 219 g) injected with 137Cs it was demonstrated that there is a dose response relationship of the amount of radiation elimination with Prussian blue insoluble doses from 1 to 50 mg/day. There was a little difference in radiation elimination rate between Prussian blue insoluble doses of 50 to 100 mg/day. In Table 1, the % Injected Radiation Dose Remaining is defined as the percentage of the total injected dose of 137Cs remaining in the body at 96 hours post administration.

Data from additional literature articles including a study of 7 human volunteers contaminated with trace doses of 137Cs and reports on 19 patients contaminated with 137Cs in other incidents show a similar reduction in whole body effective half-life after Prussian blue insoluble treatment.

Thallium Contamination
Thirty-four patients treated with Prussian blue insoluble for non-radioactive Thallium poisoning are reported in the literature. Prussian blue insoluble treatment reduced the mean serum biologic half-life of Thallium from 8 days to 3 days.

INDICATIONS AND USAGE
Prussian blue insoluble is indicated for treatment of patients with known or suspected internal contamination with radioactive Cesium and/or radioactive or non-radioactive Thallium to increase their rates of elimination.

CONTRAINDICATIONS
None

WARNINGS
Prussian blue insoluble is administered to decrease radiation exposure. It does not treat the complications of radiation exposure. Patients contaminated with high doses of 137 Cs may develop radiation toxicity including bone marrow suppression with severe neutropenia and thrombocytopenia. Supportive treatment for radiation toxicity symptoms should be given concomitantly with Prussian blue insoluble treatment.

In radiological emergencies, the type of elemental exposure may not be known. Prussian blue insoluble may not bind to all radioactive elements and some radioactive elements may not undergo enterohepatic circulation, which is needed for Prussian blue insoluble binding and elimination. Patients contaminated with unknown or multiple radioactive elements may require treatment with other agents in addition to Prussian blue insoluble.

PRECAUTIONS
General: Gastrointestinal
Prussian blue insoluble can cause constipation. Decreased gastrointestinal motility will slow the transit time of 137Cs bound to Prussian blue insoluble in the gastrointestinal tract, and may increase the radiation absorbed dose to the gastrointestinal mucosa. Constipation occurring during Prussian blue insoluble treatment may be treated with a fiber based laxative and/or a high fiber diet. Prussian blue insoluble should be used with caution in patients with disorders associated with decreased gastrointestinal motility.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (Years)</th>
<th>Prussian blue insoluble dose (grams/day)</th>
<th>No. of Prs</th>
<th>During Prussian blue insoluble Treatment - 137Cs ( T_{1/2} )</th>
<th>Off Prussian blue insoluble Treatment - 137Cs ( T_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>&gt;18</td>
<td>10</td>
<td>5</td>
<td>20 ± 6 days</td>
<td>80 ± 14 days (22 adult patients)</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt;18</td>
<td>6</td>
<td>10</td>
<td>25 ± 15 days</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>12 - 14</td>
<td>3</td>
<td>6</td>
<td>25 ± 7 days</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>4 - 9</td>
<td>+3</td>
<td>7</td>
<td>24 ± 2 days</td>
<td>42 ± 4 days</td>
</tr>
</tbody>
</table>

Table 1: Injected Radiation Dose Remaining as compared to being off treatment.

Figure 1: Comparisons of 137Cs whole body activity during and after Prussian blue insoluble treatment.

Line A: 137Cs whole body activity (kBq) DURING Prussian blue insoluble treatment (10 g/day).

Line B: 137Cs whole body activity (kBq) AFTER Prussian blue insoluble treatment

Dotted line: Extrapolated decrease in 137Cs whole body activity (kBq) if Prussian blue insoluble treatment was continued.
Information for Patients

Cesium-137 is excreted in the urine and feces. 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 gets onto clothing, such clothing should be washed separately.

Parents and child-care givers should take extra precaution in handling the urine and feces of pediatric patients. Care is intended to prevent re-exposure to the adult and pediatric patient.

In patients with constipation, a fiber based laxative and/or high fiber diet is recommended during treatment with Prussian blue insoluble. Patients taking Prussian blue insoluble should be informed that their stools might be blue-colored.

In patients who cannot swallow capsules, when the capsules are opened and the contents are mixed with food and eaten, the mouth and teeth might be colored blue.

Laboratory Tests

Prussian blue insoluble may bind electrolytes found in the gastrointestinal tract. Asymptomatic hypokalemia, with serum potassium of 2.5 – 2.9 (normal 3.5 – 5.0), was reported in 3/42 (7%) of patients on treatment with Prussian blue insoluble. Serum electrolytes should be closely monitored during Prussian blue insoluble treatment. Caution should be exercised when treating patients with pre-existing cardiac abnormalities or electrolyte imbalances. Prussian blue insoluble may bind some orally administered therapeutic drugs. As appropriate, blood levels or clinical response to oral medications should be monitored.

Drug-Drug Interactions

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. In preliminary studies, animals were contaminated with several different radioisotopes and treated with several different radiolarians. Based on these animal data, co-administration of Prussian blue with other radioeluminators does not affect the efficacy of Prussian blue for 137Cs.

Binding to some therapeutic drugs and essential nutrients is possible. The literature contains anecdotal reports of asymptomatic hypokalemia and decreased bioavailability of oral tetracycline. The serum levels and/or clinical response to critical orally administered products should be monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Prussian blue insoluble to evaluate carcinogenesis, mutagenesis and impairment of fertility have not been performed.

All males who received a whole body radiation absorbed dose greater than 1 Gy of Cs-137, 2 – 8 years later had either oligospermia or azoospermia.

Pregnancy Category C

Comprehensive animal reproductive studies have not been conducted with Prussian blue insoluble. Since Prussian blue insoluble is not absorbed from the gastrointestinal tract, effects on the fetus are not expected. In one patient that became pregnant 3 years and 8 months after being treated with Prussian blue insoluble for internal contamination with 137Cs (8 mCi), complications or birth defects were not identified in the literature report.

Cesium-137 is known to cross the human placenta. One patient, in Goiânia, was contaminated with 0.005 mCi/137Cs during her 4th month of pregnancy. She was not treated with Prussian blue insoluble. At birth the concentration of 137Cs was the same in the mother and the infant. Thallium crosses the human placenta. Reported fetal effects in the reviewed literature include fetal death, failure to thrive, alopexia, or in some instances outwardly normal development. The risk of toxicity from unretreated radioactive cesium or Thallium exposure is expected to be greater than the reproductive toxicity risk of Prussian blue insoluble.

Nursing Mothers

Studies to determine if Prussian blue insoluble is excreted in human milk have not been conducted. Since Prussian blue insoluble is not absorbed from the gastrointestinal tract, its excretion in milk is highly unlikely. However, cesium and Thallium are transmitted from mother to infant in breast milk. Women internally contaminated with Cesium or Thallium should not breast feed.

Pediatric Use

The safety and efficacy of Prussian blue insoluble and its dosing for the pediatric population was extrapolated from adult data and supported by pediatric patients who were internally contaminated with 137Cs and treated with Prussian blue insoluble in the Goiânia accident.

Overall, 27 pediatric patients received Prussian blue insoluble in the range of 0.3 – 10 grams per day in divided doses. Prussian blue insoluble treatment reduced the whole body effective half-life of 137Cs by 46% in adolescents and by 43% in children aged 8 to 12 years of age. In 12 patients for whom the rate of radiation elimination data are available, the rate was similar to that in adults treated with 3 grams TID and in pediatric patients treated with 1 gram TID. (See CLINICAL PHARMACOLOGY, Clinical Trials, Table 2.) By body weight, the dose ranged from 0.32 gram/kg in the 12-year old patient (50 gram Prussian blue daily dose, 31 kg weight) to 0.21 gram/kg in the 4 year old patient (3 gram Prussian blue daily dose, 14 kg weight).

Pediatric patients aged 2 up to 4 years are expected to have biliary and gastrointestinal function that is comparable to a 4-year old.

There are variations in the developmental maturity of the biliary system and gastrointestinal tract of neonates and infants (0 – 2 years). The dose-related adverse effects of Prussian blue insoluble on an immature gastrointestinal tract are not known. Dosing in infants and neonates has not been established.

ADVERSE REACTIONS

Deaths or serious or severe adverse events attributed to Prussian blue insoluble have not been reported.Constipation was reported in 10/42 (24%) patients in the Goiânia accident treated with Prussian blue insoluble. Severe constipation was mild in 7 patients and moderate in 3 patients. Constipation was successfully treated with a high fiber diet.

Unexplained gastric distress was reported in 3 patients treated with 20 gram/day of Prussian blue insoluble. In these patients the dose was reduced to 10 gram/day for continued treatment.

OVERDOSAGE

The clinical effects of overdosing with Prussian blue insoluble are not known. Based on reported adverse events and mechanism of action, possible overdose symptoms may include obstruction, obstruction, or severe decrease in electrolytes.

DOSE AND ADMINISTRATION

Adults and Adolescents:

The recommended dose of Prussian blue insoluble is 3 grams orally three times a day.

Pediatrics (12 – 12 years):

The recommended dose of Prussian blue insoluble is 1 gram orally three times a day.

In patients who cannot tolerate swallowing large numbers of capsules, the capsules may be opened and mixed with bland food or liquids. This may result in blue discoloration of the mouth and teeth. Prussian blue insoluble capsules may be taken with food to stimulate excretion of Cesium or Thallium.

Treatment with Prussian blue insoluble for radioactive Cesium (137Cs) contamination:

Treatment with Prussian blue insoluble should be initiated as soon as possible after contamination is suspected. Contamination should be verified as soon as possible. However, even when treatment cannot be started right away, patients should be given Prussian blue insoluble as soon as it becomes available. Treatment with Prussian blue insoluble is still effective even after time has elapsed since exposure.

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 judgment of the attending physician. Before, during and after therapy, pertinent measurements for radioactivity should be made to help determine when to terminate treatment.

During treatment, the following information should be collected:

• the radioactivity counts in urine and fecal samples should be measured and recorded weekly to monitor 137Cs elimination rate, and
• the occurrence of any adverse events from Prussian blue insoluble (i.e., constipation, which can be treated by increasing the amount of fiber in the diet).

When the internal radioactivity is substantially decreased, the Prussian blue insoluble dose may be decreased to 1 or 2 grams TID to improve gastrointestinal tolerance.

Treatment with Prussian blue insoluble for Thallium contamination:

Treatment with Prussian blue insoluble should be initiated as soon as possible after contamination is suspected. Contamination should be verified as soon as possible. However, even when treatment cannot be started right away, treatment with Prussian blue insoluble is effective and should not be withheld.

Further considerations for radioactive Cesium contamination

1. Health professionals should follow appropriate radiation protective attire and procedures at all times. Protect health professionals by handling patients from unnecessary radiation exposure and monitor health professionals and the area of operation for radiation levels, using radiation detection, indication, and computation devices (RADIAC) or thermal luminescent devices (TLD). Control spread of radiation contamination through the establishment of a patient triage site, patient decontamination area, and a contaminated or “dirty” material dumpsite. Proper labeling, handling, and disposal of contaminated material needs to be established and followed.

2. Manage the patient to minimize further injury and to stabilize before external decontamination.

3. Establish if the patient suffers from a single or combined injury (e.g., radiation, burns, trauma, chemical, biological, etc.) and whether the contaminant may be internalized.

4. The route of entry of the radiation contaminant needs to be identified and recorded. The route of entry will determine other treatment methods needed (e.g., wound debridement or stomach lavage if ingested). Patients need to be triaged based on their injuries and the level and type of contamination.

5. A quantitative baseline of the internalized contamination of 137Cs should be obtained by appropriate whole-body counting and/or by bioassay (e.g., Biodosimetry), or feces/urine sample whenever possible to obtain the following type of information to establish an elimination curve: the estimated internalized radiation contamination of 137Cs, the rate of measured elimination of radiation in the feces.

Further considerations for Thallium contamination (radioactive and non-radioactive)

General therapy guidelines for Thallium contamination should follow the radioactive decontamination procedures listed above for 137Cs, except that there is no need for radiation safety precautions when treating patients contaminated with non-radioactive Thallium. For both radioactive and nonradioactive Thallium contamination, a quantitative baseline of the internalized Thallium contamination should be ascertained by appropriate whole body counting and/or by bioassay whenever possible.

Further considerations for Thallium intoxication (radioactive and non-radioactive)

In cases of severe Thallium intoxication, additional types of elimination treatment may be necessary, such as:

• Induced emesis, followed by gastric intubation and lavage.
• Forced diuresis until urinary Thallium excretion is less than 1 mg/24h.
• Chemical hemoperfusion may be useful during the first 48 hours after Thallium ingestion (biotransformation phase).
• Hemodialysis has also been reported to be effective in Thallium intoxication.

Considerations for multiple contaminant exposure (radioactive and non-radioactive) in patients who have contamination with multiple or unknown radioactive isotopes, additional decontamination and treatment procedures may be needed.

HOW SUPPLIED

Radiogelade® (Prussian blue insoluble capsules) is supplied as 0.5 gram blue powder in gelatin capsules for oral administration packaged in brown glass bottles containing 30 capsules each. The product is manufactured by Haupt Pharma Berlin GmbH for distribution by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Berlin.

NDC 58060-002-01

Storage

Store in the dark at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

PATIENT TREATMENT DATA

To develop long-term response data, detailed information on patient treatment should be provided to the manufacturer whenever this drug is administered. 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 (see attached patient data form). In cases where exposure is limited in terms of number of patients, it may be possible to collect more detailed patient information. Please see the following website, www.heylex.com for additional suggested data collection.

Questions regarding patient treatment data collection and the use of Prussian blue insoluble for the treatment of patients exposed to radioactive Cesium and/or radioactive or nonradioactive Thallium may be submitted to:

Dr. Johann Ruprecht, Email: info@heylex-berlin.de, Fax +49 30 817 4049

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