DRAFT LABELING

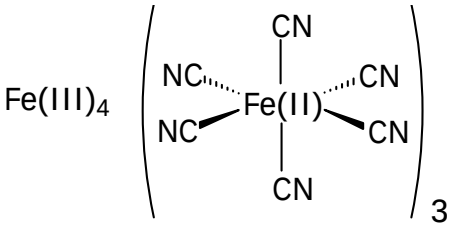
(Insert tradename _____)

Insoluble Prussian blue capsules

For Oral Administration

DESCRIPTION

Prussian blue capsules contain insoluble ferric hexacyanoferrate(II), with an empirical formula of Fe_4 $[Fe(CN)_6]_3$ and a molecular weight of 859.3 Daltons. It is provided as a blue powder in 0.5 gram gelatin capsules without other drug excipients. The structural formula is shown below.



CLINICAL PHARMACOLOGY

General

Insoluble Prussian blue, Ferric(III) hexacyanoferrate(II), after oral ingestion is not absorbed through the intact gastrointestinal wall. Its clearance from the body depends on the gastrointestinal tract transit time. Prussian blue acts as an ion-exchange medium and has a very high affinity for radioactive and non-radioactive cesium and thallium.

Prussian blue irreversibly binds cesium and thallium isotopes that are in the gastrointestinal tract after ingestion or biliary excretion. In studies of rats, pigs, and dogs that were internally contaminated with cesium and thallium, the presence of the insoluble complexes in the gastrointestinal lumen, changed the primary elimination route from the kidney to the feces and increased the rate of elimination of these two contaminants.

The rate of cesium and thallium elimination was proportional to the duration and dose of Prussian blue. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics)** A radioactive element has a constant rate of disintegration that is reflected by its physical half-life. The rate of element elimination from the body is reflected by its biologic half-life. The combined rate of radiation disintegration and rate of element elimination is reflected by the effective half-life.

Cesium-137 (^{137}Cs) has a physical half-life of 30years with a Beta energy peak at 174.0 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 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 (^{201}Tl) has a physical half-life of 3 days with energy electron, photon, and gamma (energy peak at 167.4 keV) emissions. Following entry into the blood, thallium is distributed in the kidneys (3%) and all other organs (97%). Non-radioactive thallium, depending upon the tissue, has a biological 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 treatment, the fecal to urine excretion ratio of thallium is approximately 2:1. Because Thallium's physical half-life is shorter than the biologic half-life, the rate of element elimination is critical.

Based on the ion exchange mechanism and chemical characteristics, Prussian blue may bind other elements (e.g., potassium), and cause electrolyte or other nutritional imbalances. (See **PRECAUTIONS**.)

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 ^{137}Cs it was demonstrated that there is a dose response relationship of the amount of radiation elimination with Prussian blue doses from 1 to 50 mg/day. There is little difference in radiation elimination rate between Prussian blue doses of 50 to 100 mg/day. In Table 1, the *% of Injected Radiation Dose Remaining* is defined as the percentage of the total injected dose of ^{137}Cs remaining in the body at 96 hours post administration.

Table 1: Dose Response Relationship in Rats at 96 Hours

Prussian blue Dose (mg/day)	**% Injected ^{137}Cs Dose Remaining (Range)**
Untreated	58.1 (63.3 – 53.4)
1	9.42 (13.2 – 6.72)
10	1.17 (1.64 – 0.84)
50	0.57 (0.80 – 0.41)
100	0.52 (0.73 – 0.37)

Human Data: The results of fecal analysis from those patients contaminated with ^{137}Cs and treated with Prussian blue showed higher activities of ^{137}Cs in feces, and the associated whole

body radioactivity counts showed a more rapid rate of elimination from the body. The effectiveness of Prussian blue for one patient is shown in Figure 1. The whole body content of radioactive material of ^{137}Cs in kilo-Bequerels (kBq) is on the *y*-axis. Time in days is on the *x*-axis. Line "A" represents the content of ^{137}Cs during Prussian blue treatment of 10 gm daily. The dotted line represents extrapolation if treatment was continued. Line "B" represents the content of ^{137}Cs, after Prussian blue was stopped.

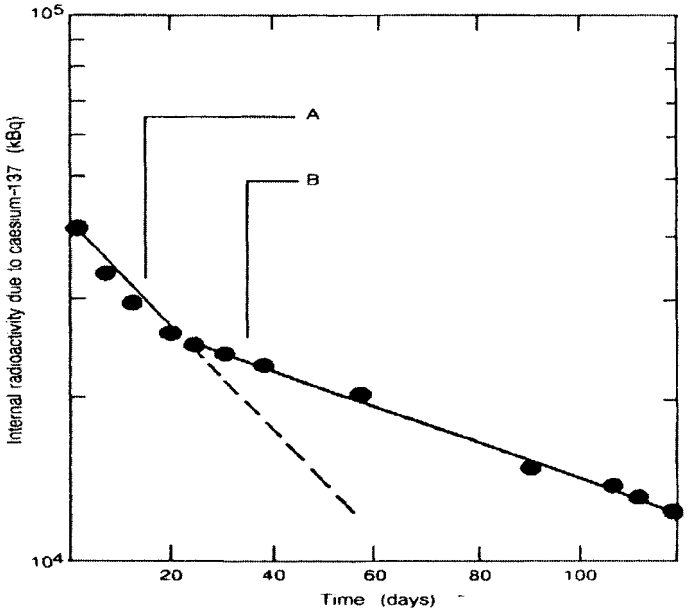


Figure 1. Comparisons of whole body ^{137}Cs radiation content during and after Prussian blue treatment.

Line A: ^{137}Cs whole body radiation content (kBq) DURING Prussian blue 10 gm/day.

Line B: ^{137}Cs whole body radiation content (kBq) AFTER Prussian blue treatment is terminated.

Dotted line: Extrapolated decrease in ^{137}Cs whole body radiation content (kBq) if PB treatment was continued.

Pharmacokinetics

Absorption/Elimination

In animal studies of pigs (n= 38), after a single dose of 40 mg of labeled Prussian blue, 99% of the administered PB dose was excreted unchanged in feces. Absorption from multiple doses has not been studied.

Food Effects

Food effect studies were not identified in the literature. In animal studies, Prussian blue was not significantly absorbed. Prussian blue's affinity for cesium and thallium is greater than its affinity for nutritional elements. Food is not expected to appreciably interfere with Prussian blue's ability to rapidly eliminate cesium or thallium.

Food is known to increase bile production and enterohepatic circulation. The increase in enterohepatic circulation may increase the amount of cesium and thallium in the gastrointestinal lumen, and may increase the amounts available for binding with Prussian blue. Prussian blue may dissociate at very low pH levels (<1 pH) and release cyanide, which may be absorbed. The dissociation may decrease Prussian blue's binding capacity for cesium and thallium and, thereby,

decrease its efficacy. Food is known to increase the pH of gastric and intestinal contents; therefore lowering the risk of dissociation.

Renal Impaired and/or Compromised Liver Function Patients

Adequate and well-controlled pharmacokinetic and pharmacodynamic studies in renal impaired and/or compromised liver function patients were not identified in the literature. Prussian blue is not systemically bioavailable and does not rely on renal elimination or hepatic metabolism; therefore, the use of Prussian blue is not contraindicated in these groups of patients.

Clinical Trials

Epidemiological studies and literature review data were reported in 106 subjects who received Prussian blue after excessive exposure to cesium-137 or non-radioactive thallium.

Cesium Contamination

Overall, in literature reports, 65 patients and 7 normal human volunteers received Prussian blue after internal contamination with ^{137}cesium (Cs).

In a 1987 incident in Goiânia, Brazil, 46 persons with heavy internal contamination with ^{137}Cs were treated with Prussian blue. Data on the whole body effective half-life of ^{137}Cs, during treatment and after Prussian blue treatment was completed on 33/46 of these patients. The untreated mean whole body effective half-life of ^{137}Cs 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 ^{137}Cs by 69% in adults, by 46% in adolescents and by 43% in children. The following table shows the decrease in whole body effective half-life of ^{137}Cs in patients during Prussian blue treatment as compared to being off treatment.

Table 2: ^{137}Cesium Effective Half-life During and After Treatment with Prussian Blue (In Days, by Age, and Dose of Prussian Blue)

Group	Age (Years)	Prussian blue dose (Grams/day)	No. of Pts.	During Prussian blue Treatment - ^{137}Cs $T_{1/2}$	Off Prussian blue Treatment - ^{137}Cs $T_{1/2}$
Adults	> 18	10	5	26 ± 6 Days	80 ± 15 Days (all 21 adult patients)
Adults	> 18	6	10	25 ± 15 Days	
Adults	> 18	3	6	25 ± 9 Days	
Adolescents	12 -14	< 10	5	30 ± 12 Days	62 ± 14 Days
Children	4 - 9	< 3	7	24 ± 3 Days	42 ± 4 Days

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

Thallium Contamination

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

INDICATIONS AND USAGE

Prussian blue 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 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 treatment.

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

Prussian blue dissociates and becomes inactive in very acidic environments (e.g., pH of 0 to 1) and may release cyanide. Patients with disorders associated with hypersecretory states (e.g., gastrinemia, Zollinger-Ellison Syndrome) may have extremely low gastric pH levels for extended periods of time. Prussian blue may not be effective and there may be a risk of cyanide poisoning in these patients. When possible, the gastric acidity should be stabilized at higher pH levels before administering Prussian blue.

PRECAUTIONS

General: *Gastrointestinal*

Prussian blue can cause constipation. Decreased GI motility will slow the transit time of ^{137}Cs bound to Prussian blue in the GI tract, and may increase the radiation absorbed dose to the GI mucosa. Constipation occurring during Prussian blue treatment may be treated with a fiber

based laxative and/or a high fiber diet. Prussian blue should be used with caution in patients with disorders associated with decreased GI motility.

Information for Patients

^{137}Cesium 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.

Patients taking Prussian blue should be informed that their stools might be blue-colored.

Laboratory Tests

Prussian blue may bind electrolytes found in the GI tract. Asymptomatic hypokalemia, with serum potassium values of 2.5-2.9 (normal 3.5-5.0), was reported in 3/42 (7%) of patients on treatment with Prussian blue. Serum electrolytes should be closely monitored during Prussian blue treatment. Caution should be exercised when treating patients with pre-existing cardiac arrhythmias or electrolyte imbalances.

Prussian blue 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 radioprotectants. Based on these animal data, co-administration of PB with other radioprotectants does not affect the efficacy of PB for ^{137}Cs.

PB ion exchange capacity is a function of the atomic volume, electronic charge, and other chemical characteristics. Binding to some therapeutic drugs and essential nutrients is possible. The literature contains anecdotal reports of asymptomatic hypokalemia and decreased bioavailablity 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 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 ^{137}Cs, 2-8 years later had either oligospermia or azospermia.

Pregnancy Category C

Comprehensive animal reproductive studies have not been conducted with Prussian blue. Since Prussian blue 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 for internal contamination with ^{137}Cs (8 mCi), complications or birth defects were not identified in the literature report.

^{137}Cesium is known to cross the human placenta. One patient, in Goiânia, was contaminated with 0.005 mCi ^{137}Cs during her 4th month of pregnancy. She was not treated with Prussian blue. At birth the concentration of ^{137}Cs 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, alopecia, or in some instances outwardly normal development. The risk of toxicity from untreated radioactive cesium or thallium exposure is expected to be greater than the reproductive toxicity risk of Prussian blue.

Nursing Mothers

Studies to determine if Prussian blue is excreted in human milk have not been conducted. Since Prussian blue is not absorbed from the gastrointestinal tract, its appearance 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 and its dosing for the pediatric population was extrapolated from adult data and supported by pediatric patients who were internally contaminated with ^{137}Cs and treated with Prussian blue in the Goiânia accident.

Overall, 27 pediatric patients received Prussian blue in the range of 3 – 10 grams per day in divided doses. Prussian blue treatment reduced the whole body half-life of ^{137}Cs by 46% in adolescents and by 43% in children aged 4 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 **CLINCIAL PHARMACOLOGY, Clinical Trials,** Table 2.) By body weight, the dose ranged from 0.32 gram/kg in the 12-year old patient (10 gram PB daily dose, 31 kg weight) to 0.21 gram/kg in the 4 year old patient (3 gram PB 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 pre-natal, neo-natal, and infants (0-2 years). The dose-related adverse effects of Prussian blue 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 have not been reported Constipation was reported in 10/42 (24%) patients in the Goiânia accident treated with Prussian blue. Severity of constipation was mild in 7 patients and moderate in 3 patients. Constipation was successfully treated with a high fiber diet.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

THE MAIN TREATMENT OBJECTIVE IS TO REDUCE INTERNAL CONTAMINATION OF CESSIUM AND THALLIUM BY PREVENTING FURTHER INTAKE, REDUCING DEPOSITION, AND INCREASING THE RATE OF EXCRETION.

In patients who cannot tolerate swallowing large numbers of capsules, the capsules may be opened and mixed with bland food or liquids.

Prussian blue capsules should be taken with food to stimulate excretion of cesium or thallium and to avoid low gastric pH (see **WARNINGS**). Patients receiving Prussian blue should be instructed to use appropriate measures to promote regular fecal elimination.

Adults and Adolescents:
The recommended dose of Prussian blue is 3 grams orally three times a day.

Pediatrics (2 - 12 years):
The recommended dose of Prussian blue is 1 gram orally three times a day.

Treatment with Prussian blue for radioactive cesium (^{137}Cs)contamination:

Treatment with Prussian blue 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 as soon as it becomes available. Treatment with prussian blue 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 judgement 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 ^{137}Cs elimination rate, and
- the occurrence of any adverse events from Prussian blue (i.e., constipation, which can be treated by increasing the amount of fiber in the diet).

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

Treatment with Prussian blue for thallium contamination:

Treatment with Prussian blue 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 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 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. 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.

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.

3. MANAGE THE PATIENT TO MINIMIZE FURTHER INJURY AND TO STABILIZE BEFORE EXTERNAL DECONTAMINATION.

4. A quantitative baseline of the internalized contamination of ^{137}Cs 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:
    - Estimated internalized radiation contamination of ^{137}Cs, and
    - 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 ^{137}Cs, except that there is no need for radiation safety precautions when treating patients contaminated with non-radioactive thallium. For both radioactive and non-radioactive thallium contamination, a quantitative baseline of the internalized thallium contamination should be ascertained by appropriate whole-body counting and/or by bioassay whenever possible.

Patients should also have weekly CBC, serum chemistry and electrolytes while under treatment. The response to other orally administered medications should be closely monitored. (See **Drug-Drug Interactions.**)

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 (8-12 1/24h) until urinary thallium excretion is less than 1 mg/24h.
- Charcoal hemoperfusion, may be useful during the first 48 hours after thallium ingestion (biodistribution 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 more than cesium and thallium, additional decontamination and treatment procedures may be needed.

HOW SUPPLIED

(Insert tradename _____) is supplied as 0.5 gram blue powder in gelatin capsules for oral administration. The product is supplied by (insert name and location _____).

NDC# XXXXX-XXX-XX

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 and information on the risk of developing late malignancy detailed information on patient treatment should be provided to the manufacturer. 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.

Questions regarding the use of Prussian blue for the treatment of radioactive or non-radioactive thallium and/or cesium may be referred to

(Insert Name and contact information)_____