

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-626

ADMINISTRATIVE DOCUMENTS

Reistötter, Kinzebach & Partner
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To the
U.S. Department of Health and
Human Services
Food and Drug Administration

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Dr. Peter Riedl
Dr. Georg Schweiger
Dr. J. Uwe Müller
Dr. Wolfgang Thalhammer
Dr. Michael Pohl
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Sternwartstr. 4, D-81679 München
email: office@kinzebach.de

München, den 03. March 2003

Unsere Akte:
Our Ref.:

Betreff:
Re:

NDA FOR PRUSSIAN BLUE DRUG PRODUCT:
DECLARATION UNDER § 314.50

We, Reistötter, Kinzebach & Partner, are an internationally working patent law firm.
We have conducted intensive searches regarding patents that claim prussian blue or
or that claim a use of prussian blue.

We declare that, in the opinion and to the best knowledge of HEYL Chemisch-
pharmazeutische Fabrik GmbH & Co. KG on which behalf we act, there are no
patents that claim the drug or drugs on which investigations that are relied upon in
this application were conducted or that claim a use of such drug or drugs.

Dr. Thomas Wolter

Dr. Thomas Wolter
European Patent Attorney
Reistötter, Kinzebach & Partner

2510/mm

MÜNCHEN

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EXCLUSIVITY SUMMARY for NDA # 21-626 SUPPL # N/A
Trade Name Radiogardase
Generic Name insoluble Prussian blue
Applicant Name Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
HFD-160
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/ X / NO / ___ /
b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type(SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 year marketing exclusivity

7 year orphan exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!		
IND # _____	!	YES /___/	NO /___/ Explain:
	!		
	!		
	!		
Investigation #2	!		
IND # _____	!	YES /___/	NO /___/ Explain:
	!		
	!		
	!		

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		
Investigation #2	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Lynn Panholzer, Pharm.D.
Signature of Preparer
Title: Consumer Safety Officer

Date September 29, 2003

Sally Loewke, M.D.
Signature of Office or Division Director

Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Sally Loewke
10/2/03 10:02:06 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-626	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Radiogardase™ (insoluble Prussian blue) 0.5gm capsule		Applicant: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
RPM: Lynn Panholzer, Pharm.D.	HFD-160	Phone # 301-827-7510
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1 (NME)
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		December 13, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified N/A

Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) (<i>indicate date of each review</i>)	PM- October 1, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	ODS tradename review- May 9, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	September 29, 2003
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X

Clinical and Summary Information

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	DD: October 2, 2003 November 26, 2002 OD: October 2, 2003 March 21, 2003 September 18, 2002
❖ Clinical review(s) (indicate date for each review)	September 15, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Div. Dir. memo Oct. 2, 2003
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	August 30, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A

CMC Information

❖ CMC review(s) (indicate date for each review)	October 1, 2003 September 29, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	October 1, 2003
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	May 29, 2003
❖ Facilities inspection (provide EER report)	Date completed: Sept. 11, 2003 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	October 2, 2003 September 4, 2003 September 23, 2002
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-626 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: March 13, 2003 Action Date: October 2, 2003

HFD-160 Trade and generic names/dosage form: Radiogardase (insoluble Prussian blue) capsules

Applicant: Hevl Chemisch-pharmazeutische Fabrik GmbH & Co. KG Therapeutic Class: IP

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: 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

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- X No: Please check all that apply: Partial Waiver X Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. 0-24 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- X Formulation needed

Other: _____

Date studies are due (mm/dd/yy): No specific date established. See attachment for description of studies and expected timeframes for completion.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Lynn Panholzer, Pharm.D.
Regulatory Project Manager

cc: NDA 21-626
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment

Pediatric studies

- a. Develop appropriate dosage form for use in younger children.
 - i. Submission of plan to develop pediatric formulation: Within 6 months of the date of the action letter
 - ii. Begin development: Within 6 months of agreement to plan
 - iii. Completion of formulation development: Within 18 months of initiation of development

- b. Studies to determine dosing for neonates to 2 years of age (based on human extrapolation and/or animal models).
 - i. Protocol submission: Within 6 months of the date of the action letter
 - ii. Study start: Within 6 months of agreement to the protocol
 - iii. Final study report submission: Within 12 months of initiation of the study

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Lynn Panholzer :
10/1/03 09:14:31 AM



Berlin, February 5, 2003

DEBARMENT CERTIFICATION STATEMENT

Heyl Chemisch-pharmazeutische Fabrik, Berlin hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Dr. Wolfgang Parr
Heyl Chemisch-pharmazeutische Fabrik
Managing Director

US Agent
Robert Z. Martin
Heyltex Corporation
Vice President Operations

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 2, 2003
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: NDA 21-626 Radiogardase 500mg capsules (insoluble Prussian blue) by HEYL
Chemish-pharmazeutische Fabrik GmbH & Co. KG.

This memo documents my concurrence with the Division of Medical Imaging and Radiopharmaceutical Drug Product's recommendation to approve Radiogardase for the 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. On February, 2003 FDA published in the Federal Register that insoluble Prussian blue was safe and effective for this indication if manufactured under specified conditions in an approved marketing application. HEYL's application cites this notice thereby obviating submission of clinical, pharm-tox, biopharm data. HEYL has provided acceptable processes and controls for manufacturing. The Office of Compliance has stated the manufacturer's plant inspection done in 2002 is acceptable.

Regulatory Time Line

This NDA was submitted on March 13, 2003 as a priority B2 application and within two weeks a list of filing deficiencies was presented to the sponsor who was able to provide data to have the application filed. This application and the administrative record will reflect considerable interaction between FDA and the sponsor to ensure missing data, clarifications, and other information were submitted to allow FDA to make an approval decision. The manufacturer's inspection was done in the summer of 2002, in anticipation of submission of this application, while the drug was being made under IND by the sponsor.

During the review cycle, several factors came to light that were not previously identified:

- Mid-way through the priority review cycle, FDA became aware that free cyanide dissociation could occur at extremely high pH. This new information impacted FDA's need to ensure that the product was safe for consumption, because the pH of the gastrointestinal tract ranges from pH 1 to 9. Additional data were needed to understand the free cyanide release profile across this pH spectrum.
- In June, 2003, FDA became aware that the physical appearance of Prussian blue varied considerably and there was concern that the "salt and pepper" appearance of the newly manufacturer batches were of different safety or effectiveness from other more uniformly dark batches.
- The mechanism of action and active moiety of insoluble Prussian blue needed to be clarified for labeling.

The new information the company submitted in response to our inquiry for data for the first two bulleted items, along with information on their manufacturing controls and processes, led to major amendment submissions that triggered the clock to be extended and FDA took 3 weeks to complete the application review, negotiate labeling, and obtain agreements on phase 4 studies.

pH and Cyanide

Prussian blue dissociates at extreme pHs and releases free cyanide. The FDA laboratories conducted testing for this, including at pHs 1 and 9 at various dwell times, to evaluate this safety risk. HEYL submitted data also at these pHs. The FDA laboratory testing results and HEYLs are not meant to replicate each other. FDA's methods differed from HEYL (see Chemistry memo). We used longer dwell times and

constant pH titration to maintain the pH throughout the testing time. These factors would make FDA values higher than HEYL's values. We selected pHs of 1 and 9 because these are the extreme pHs found in the gastrointestinal tract. The dwell times at low pH up to 24 hours were greater than would be expected for the drug to be in contact with gastric acids, which is usually up to a few hours. The dwell times of 24 hours for high pH is about the duration for the drug to be in contact with Brunner's crypts.

The values obtained for low pH at 4 hours and high pH at 24 hours show levels of free cyanide levels a few fold higher than then EPA's reference dose for lifetime oral exposure. If our cyanide release test has relevancy to clinical conditions, then this amount of cyanide exposure would be acceptable given the benefits of the drug and the duration of treatment being limited. Even at higher release, such as at 24 hours at pH 1, our estimates from rat NOAEL and the EPA reference standard show acceptable safety margin. The "salt and pepper" appearing batch that was recently manufactured was tested for cyanide release and found to be acceptable. As a caveat, we do not know the clinical relevance of the in vitro testing and results to actual human digestion and exposure. Human data from cyanide poisoning cases that resulted in death also show acceptable safety margins. Furthermore, no cases of cyanide poisoning have been reported under the IND or in the literature. Therefore, we do not believe a warning is needed on this manufacturer's drug label about cyanide poisoning. The warning may be relevant to other manufacturer's products and for other NDAs we will ask for the same types of pH, dwell times, and cyanide values to see if labeling with a warning or not is appropriate.

The release specifications for the drug product in the NDA was for _____ (not titrated or buffered to keep a constant pH). FDA tested the one hour dwell method without constant maintenance of pH at pH 1.0 for cyanide release and found that results between the two pH testings are related in a way that keeping the release criteria at 10ppm at pH 5.5 is acceptable.

Salt and Pepper Appearance of Drug Product

HEYL's recently manufactured drug product has a noticeable "salt and pepper" appearance, different from batches originally cited in the NDA during filing.

As mentioned before, the cyanide release was acceptable for these "salt and pepper" batches.

FDA labs performed cesium binding at one hour at pH 7.5 and the all drug product showed acceptable activity. In particular, the "salt and pepper" appearing batch of recently manufactured drug product was tested for binding and found to be acceptable.

Physical appearance may vary due to differences in insoluble Prussian blue particle size, amount of excipient (microcrystalline cellulose), and water content. This variation of appearance has been noted in the labeling.

Mechanism of Action

Dr. Moheb Nasr, Acting Director, Office of New Drug Chemistry, has written an extensive review on the chemical structure and mechanism of action of insoluble Prussian blue and other forms of Prussian blue. The mechanism of action for cesium binding and elimination has now been better elucidated and labeling has been updated.

Labeling

Important changes to the labeling recommended in the FDA Guidance to Industry published last February 2003 are:

- 1) **DESCRIPTION:** now includes variation in appearances, new chemical structure to show hydrous form, and information about the three-dimensional nature of the molecule as this contributes to the mode of action.
- 2) **CLINICAL PHARMACOLOGY:** the mechanisms of action has been changed from "ion exchange" to reflect the various mechanisms of action (ion exchange, adsorption, and mechanical trapping within the crystal structure), the figure's labeling has been corrected from "whole body radiation" to "whole body activity."

3) WARNINGS:

- 4) PATIENT INFORMATION DATA: We agreed upon with the company on the elements to collect in long term follow up studies as a Phase 4 study.

This NDA is approved for marketing with phase 4 studies to conduct long term follow data collection and to develop pediatric formulation and dose of the drug because it is imperative that children less than two years of age have access to this medication if they were exposed to unacceptable levels of cesium radiation.

This NDA approval conveys exclusivities for marketing to the sponsor. There is 5 year NME exclusivity and 7 year Orphan Drug exclusivity that run concomitantly. These exclusivities are incentives for the development of drugs. Consequences of these incentives include other effects such as dependence on a single manufacturer for the period in which exclusivity is granted. Therefore, if a single manufacturer has problems with drug production (from materials shortages, problems in capital investment, business decisions, etc.), this can lead to drug shortages. While Orphan exclusivity may be broken with demonstration of inability to supply the market needs after a process is followed, there is no such provision with the 5 year NME exclusivity. As this drug has use as a medical counterterrorist measure, these issues become important and require FDA to work closely with the manufacture and others for public welfare.

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Florence Houn
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2003
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo Amendment
TO: Prussian Blue

This memo documents my decisions to change the phase 4 studies being asked of sponsors of NDAs for Prussian blue. The division director memo listed five studies for post-approval investigation:

1. 
2. 
3. 
4. 
5. 

Upon further review of these studies at a meeting on March 20, 2003 by the review team, the Office of Counter Terrorism and Pediatric Programs, Office of Regulatory Policy, and the Office of Commissioner's Office of Counter-Terrorism, the studies have been revised. We also discussed that a recommended case report data collection form will be provided to sponsors to help obtain data on post-marketing experience.

Study #1 has been revised to be more general in meeting future needs for analyses for safety and effectiveness. 

The phase 4 studies are:

- Longitudinal studies involving follow up on case report forms and placement of data into a database for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
- Pediatric studies to investigate safety tolerability of dosing for neonates to 2 years of age.

Finally, this note documents that all manufacturers will be asked to provide pH dissociation of Prussian blue to cyanide prior to approval.

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Patricia Stewart

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CSO

Originally signed by Dr. Florence Houn 3/21/03

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 18, 2002
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: IND 51,700 Insoluble Prussian Blue (ferric hexacyanoferrate)

This memo documents my concurrence that sufficient data exists in the literature for the Agency to make a finding of safety and efficacy that Prussian Blue (PB) is indicated for treatment of patients with known or suspected internal contamination with radioactive and/or non-radioactive cesium or thallium to increase their rate of elimination.

This finding is primarily based on the clinical experience that occurred in Gioania, Brazil in 1987 in which 46 individuals received treatment with PB following contamination from cesium. Pharmacokinetic data and whole body counts were obtained during and after drug treatment. Effective half-lives for 137-cesium were obtained in the same patients. Reduction of this endpoint is viewed as clinically meaningful as it means less exposure to radiation. Safety information was gathered that reveals the most common side effect is constipation. PB is not absorbed.

For thallium elimination, the literature contains 3 case-studies that had a total of 34 patients and their experience. Results showed a decrease in effective half-life with drug administration. No other safety issues were reported.

The type of evidence is viewed as acceptable to the Agency for several reasons. The literature reports reviewed involved prospective data collection in a sufficient number of cases for this indication. Adequate dosing information was provided in the articles. Patients served as their own controls. Pre- and post-treatment measurement of radiation elimination (an objective endpoint) was evaluated to demonstrate efficacy. These measurements were performed using acceptable methodology. The population studied is poor and indigent patients who were heavily contaminated. Despite the delay in toxin identification and treatment initiation, the data demonstrate that for these patients there was a clear improvement in radiation elimination. It is expected that in the U.S., where medical care is more available, patient follow up, compliance with medication, and monitoring would allow for consistent treatment and dose adjustments. The data in this population provides an acceptable estimate of drug performance in less than optimal medical care circumstances with heavily contaminated individuals. Replication of findings is present in the treatment IND experience Oak Ridge has provided. These data are mostly from laboratory accidents where radioactive contamination is less.

It is not ethical to conduct human clinical trials that would involve the purposeful exposure of subjects to radiation without possible benefit. There is no ethical concurrent control to use in subjects who may be exposed on their own through accidents. Blinding of investigators is not possible given that placebo is unethical, the lack of a suitable control therapy, and the need to follow radiation counts in patients. The condition of contamination with 137-cesium and thallium is extremely rare in the US, making opportunistic data few. Nevertheless, treatment IND clinical data from Oak Ridge support the effectiveness found from the literature. Finally, the non-clinical data in the literature support the indication.

I agree that Phase 4 studies can further refine labeling but are not needed prior to approval. Labeling suggestions have been conveyed to the division.

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Patricia Stewart

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Signed by Dr. Florence Houn 9-18-02

DIVISION DIRECTOR INTERIM MEMORANDUM TO THE FILE

NDA: Pending
IND: 51,700
DRUG: Prussian Blue (Insoluble)
ROUTE: Oral capsule, 500 mg
CLASS: Radioprotectant, Decorporation, Radioeliminator
INDICATION: _____ Cesium and thallium poisoning in patients
with known or suspected exposure
SPONSOR: Radiologic Emergency Assistance Center and Training Site
(REAC/TS)
SUBMITTED: Pending
COMPLETED: September 18, 2002

RELATED DRUGS: Calcium DTPA
Zinc DTPA
Potassium iodide

RELATED REVIEWS:

Chemistry: David Place, PhD, 10/01/02 (preliminary)
Clinical: Robert Yaes, MD, PhD, 09/18/02
Clinical Pharmacology: Alfredo Sancho, PhD, 08/30/02
Microbiology: David Hussong, PhD, 05/09/02 (preliminary)
Pharmacology-toxicology: Adebayo Laniyonu, PhD, 08/09/02
Project Manager: Patricia Stewart, RTN

BACKGROUND

Prussian Blue {ferrichexacyanoferrate, $\text{Fe}[\text{Fe}(\text{CN})_6]$, or Ferric (III) hexacyanoferrate(II)} is one of several drugs receiving expedited Agency review to facilitate the availability of drugs to treat radiation emergencies. Although an NDA has not been submitted to establish safety and effectiveness, Prussian Blue has been used under an IND for several years. Initially, the Department of Energy through their subcontractor Oak Ridge Institute held the IND for _____. Subsequently, the IND was subcontracted to REAC/TS, (Radiologic Emergency Assistance Center and Training Site). Largely Prussian Blue (PB) was used to treat nuclear reactor related accidental exposure to radioactive cesium or thallium. Also, PB has been used to treat human contamination with non-radioactive thallium contained in rat poison. Studying a drug to treat radiation contamination is a challenge. Traditional randomized, controlled trials in radiation contaminated patients are considered to be unethical because withholding potentially beneficial treatment would not be appropriate. Also, over the years, the number of exposures to cesium or thallium has been relatively low. Given the low volume of use, and the ethical contradiction to conducting a controlled clinical trial in contaminated patients, a commercial sponsor did not come forward to champion drug development and approval. Instead one worldwide supplier (HEYL Chemisch-

pharmazeutische Fabrik GmbH & Co KG in Germany) provided the drug to the United States and to other countries under the name Radiogardase®. Also, several decades ago, an IND process was developed to allow PB's use in emergency situations in this country. This included a single patient case report form and dosing instructions that were printed in a manner that is analogous to an approve package insert. The results of the experience with Prussian Blue were published in the literature and form the basis of the Agency clinical, pharmacology-toxicology, and clinical pharmacology reviews. Data from the manufacturing site, HEYL, formed the basis of the Chemistry review. These reviews conclude that pending resolution of CMC deficiencies, the identification of an NDA holder, and commitments for post-approval studies, there are sufficient data to approve Prussian Blue. The recommended indication is for acute and chronic use in patients with known or suspected contamination with radioactive and non-radioactive cesium or thallium to increase their rate of contaminant elimination.

Critical aspects of the regulatory decision focused on the source of the review material, product mechanism of action, and the inability to conduct clinical trials. Substantial attention was placed on determining the dose, dose regimen, and potential use with other products. The discipline reviews (clinical, clinical pharmacology, and pharmacology-toxicology) are complete and may be read for details. Additionally, the Clinical Pharmacology and Biopharmaceutics review provides a cogent overview of radiation biology and the effects of ionizing radiation. This memorandum to the file focuses on the collective assessment and recommendations.

Drug Class: Radioprotectants are drugs that decrease the amount of radiation exposure. The term "protection" does not connote a time when the product should be used; i.e., before or after exposure. Radiation toxicity may present acutely (e.g., as bone marrow suppression) or may be delayed and result in malignancy or genetic abnormalities of the reproductive cells and evidenced in the next generation. The type, severity, and rate of onset of radiation toxicity symptoms are related to the amount, acuteness, and duration of radiation exposure. Hence, the rapid elimination of radiation is accepted as a surrogate for a decrease in risk of the radiation toxicity.

Other drugs of the Radioprotectant class include potassium iodide, and two companion drugs, calcium DTPA and zinc DTPA, that are used to rapidly eliminate other radioactive elements (e.g., plutonium, americium). In 1982, potassium iodide was approved as a radioprotectant for the thyroid gland for use "prior to and following ... a radiation emergency" to block the thyroid uptake of radioiodine and, thereby, "reduce the risk of thyroid cancer in radiation emergencies involving the release of radioactive iodine"¹. Although potassium iodide may be used prophylactically, data are not available on prophylactic use of PB. Since, PB is an ion exchange media, it can competitively bind other substances. In the absence of a large load of avidly binding Cs or Tl, the use of PB may decrease some electrolytes and may decrease absorption of some oral medications. Thus, prophylactic use may have other adverse effects.

¹ FDA Guidance: *Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies*, January 15, 2002.

It is conceivable, that in a radiation emergency, PB will be used along with all of the other radioprotectants in order to eliminate the risk from the spectrum of radioactive elements. Data showing the efficacy effects of the combination are limited, however.

Federal Radiation Emergency Response: In the event of a radiation emergency, several federal agencies are organized to respond². Under the Federal Radiologic Preparedness Coordinating Committee, these include DOE, DOD, FEMA, HHS, CDC, and FDA. Under 44 CFR 351.23(f), HHS is directed to provide guidance to state and local governments on the use of radioprotectant substances. As a step towards guidance development, the package insert will include a discussion of PB in the context of general radiation emergency care.

Chemistry and Mechanism of Action: Prussian Blue (PB) is an insoluble, blue powder of ferrichexacyanoferate with a molecular weight of 859.3 Daltons. The final drug product is 500 mg of PB in a gelatin capsule. PB is very dry substance that is produced with relatively standard methods, has minimal need for sterility measures once the final product is complete, and is stable for decades. The inspections of HEYL and related subcontractors are scheduled for August, 2002.

Prussian Blue is proposed for use as 500 mg capsules administered as 3 grams (6 capsules) three times a day initially, and 1 gram three times a day for maintenance. Doses up to 20 grams a day have been reported in the literature.

Prussian Blue essentially is an ion exchange medium that has a high affinity for cesium (Cs) and thallium (Tl). ¹³⁷Cesium is a common by-product of nuclear fission and it is found in sealed radiation sources used in radiation oncology treatments. The natural radioactive disintegration (the physical $t_{1/2}$) of cesium is greater than 30 years. In the body, the rate of elimination of the metal itself (the biologic $t_{1/2}$) suggests a three compartment model: i.e., with 10% eliminated in 2 days, \approx 90% in 110 days, and $<$ 1% eliminated in 500 days. In the body, because of the long physical $t_{1/2}$, the rate of radiation elimination (effective $t_{1/2}$) largely is reflected by the biologic $t_{1/2}$. Because the radiation is most toxic, its elimination is used as the outcome measure.

Thallium in its non-radioactive form is used in rodent poisons and has been the source of intentional and unintentional human poisoning. In its radioactive form, thallium has a physical $t_{1/2}$ of 3 days and is used in medical imaging. Thallium's elemental elimination from the body (the biologic $t_{1/2}$) is about 8 – 10 days. Therefore, the cold thallium is of greatest concern. The measured elimination of cold thallium is used as the outcome measure.

PB ion exchange binding is based on the atomic volume and electronic charge of the element. In addition to cesium and thallium, PB is expected to bind other elements such

² 44 CFR 351

as rubidium and francium. However, studies of PB binding to other elements in the periodic table were not identified in the literature. Additionally, the mechanism of action should allow PB to bind nutrients and therapeutic drugs with appropriate chemical characteristics. Anecdotal reports of hypokalemia and lower blood levels of tetracycline in association with PB co-administration have been reported in the literature.

PB itself is not absorbed and it does not interact with the body constituents. More specifically, in routinely administered doses, any absorption is less than the lower level of detection. In animal models, 99% of the administered dose was eliminated in the feces. The amount of diffusion through damaged gastrointestinal mucosa is not known.

PB contains cyanide, however, the compound is insoluble and could dissociate only in a media with a pH much less than 1 with an associated absence of oxidizing elements. Patients with a gastrinoma or Zollinger Ellison syndrome and gastric acid hypersecretion may have a pH of 1.5 – 2.5. Such low pHs would be associated with clinically severe ulcerations and pain that would cause the patients to seek medical attention. PB does not dissociate in milk, water, acidic juices because their pH is considerably higher. Animal toxicology studies of PB as currently manufactured did not reveal evidence of cyanide toxicity. Therefore, with appropriate dissociation manufacturing release specifications, cyanide dissociation should be prevented.

Effectiveness: As noted in all the discipline reviews, without the administration of PB, Cesium and thallium have an active enterohepatic circulation process, but are eliminated primarily through the kidneys (>80%). PB irreversibly binds the Cs and Tl that are in the GI tract after enterohepatic circulation and converts the primary route of elimination to the feces. The benefit of GI elimination is that all routes of Cs and Tl exposure (oral, inhalation, systemic) can be treated with PB. Elimination does not require normally functioning kidneys, it does not require substantial hydration and potential bladder irrigation to increase the rate of elimination through the urine, and oral administration is a convenient dosing form. By interrupting the enterohepatic recirculation process, PB increased the rate of elimination, thereby, reducing the radiation exposure time.

Animal data show that in comparison to controls, the amount of radiation eliminated increased with doses from 1 mg to 100 mg. As shown in the following table, after 4 days untreated rats had 58% of the injected dose remaining. In treated rats, depending upon the dose, the percent of remaining radiation ranged from approximately 9% to 0.5%.

PB 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)

*Derived from Dr. Laniyonu's review tables page 6

After exposure, it appears that treatment should continue as long as enterohepatic circulation effects continue. If the radioactive element becomes bound to the bone, the beneficial effects are not clear.

Data to establish the efficacy and safety of PB are derived from literature reports of 106 patients who received PB after CS or TI exposure. The most comprehensive data were contained in a retrospective, epidemiological report of the results of 46 patients that were exposed to massive doses of ¹³⁷Cs after a sealed source was breached in Gionna Brazil, 1987. The clinical review assessed several literature references that considered different aspects of the 46 patients including dosimetry, clinical findings of cesium radiation toxicity, responses to PB treatment, etc. Collectively these data support the Agency labeling revisions.

¹³⁷Cesium contamination: Overall, 46 of the most heavily contaminated patients were treated with PB. Data on the effective whole body half-life of ¹³⁷Cs, during treatment and after PB treatment were reported on 33/46 of these patients. For cesium that is not irreversibly incorporated in the body, the untreated elimination of half-life of ¹³⁷Cs is 80 days in adults, 62 days in adolescents, and 42 days in children. Prussian Blue reduced the average whole body half-life of ¹³⁷Cs by 69% in adults, by 46% in adolescents and by 43% in children. The following table shows the decrease in whole body half-life of ¹³⁷Cs in patients on and off treatment of PB. These data were derived from patients who were sequentially treated for approximately 25 days; then after treatment stopped, their measurements were followed for approximately 42-80 days.

Group	Age	PB grams/day	No. of Pts.	¹³⁷ Cs T _{1/2} On PB	¹³⁷ Cs T _{1/2} After PB
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

* Reproduced from Dr. Yaes' review page 15.

For further discussion of the response in pediatric patients, see the pediatrics section below.

Dr. Yaes, also summarized 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 half-life after Prussian Blue treatment.

Thallium contamination: Thallium was a component of rodent poison and human contamination was usually based on occupational exposure, or intentional poisoning. In recent years because of the removal of thallium from rodent poisons, the occurrence of thallium contamination in this country is decreasing. However, current literature (2000) contains isolated US reports and reports of contamination from other countries. However, most of the reported literature references are old. Dr. Yaes' identified reports of 34 patients with thallium poisoning and Prussian Blue treatment. In these patients without treatment the thallium serum biologic half-life was 8 days. On Prussian Blue 10 mg BID, the thallium serum half-life decreased to 3 days. The benefit of Prussian Blue seems to correlate with the degree of contamination and the duration of contamination. In severe toxicity, although the thallium rate of elimination increased, the existing clinical damage was not reversible. Dose response relationships appear to be similar to that of PB with ¹³⁷Cs. However, because thallium contamination is not radioactive, other elimination methods can be used as well; e.g., charcoal hemoperfusion, hemodialysis, gastric lavage.

Safety: The primary toxicity of PB is constipation and unspecific gastrointestinal distress. According to Dr. Yaes' review, this was more evident at high doses of 20 grams per day and responded to treatment with fiber.

Dose selection: The above articles on the use of PB in ¹³⁷Cs and in Tl contamination all used a divided dose (TID or BID). Also, in most instances it appears that PB was given with or after meals. In the Goiania accident dosing was with either 3, 6, or 10 mg divided three times. Although the dose was increased based on total exposure, the specific basis for selection was not described in the article. In four patients, the dose was

increased to 20 gm a day. However, gastrointestinal distress developed and the dose was returned to 10gm a day (divided). Data are not available in these 4 patients on the comparative elimination rate on 10 and 20 grams. However, the animal data shown in table 2 above shows that the greatest difference in elimination is between 1 and 10 gram per day. Limited improvement occurred after 50 and 100 gm per day.

Overall, in a radiation emergency, roughly 10 mg per day is the preferred regimen. However, splitting this dose is not simple (e.g., 10 mg TID would be 3.5, 3.5 and 3 grams or 7, 7 and 6 tablets). Alternatively, 9 grams a day would be 3 grams TID or 6, 6 and 6 tables. A dose response difference is not expected between 9 and 10 grams. Pragmatically, the recommendation is PB 9 grams (3 grams TID).

Duration of treatment: Data to justify the duration of treatment are limited. Patients were treated for 1 month to 4 years. Although the length of treatment appeared to be based on initial exposure and the continuation of radiation elimination in the feces, the criteria for continuation were not published. The primary considerations for the initiation of treatment, is the suspicion of exposure. It is critical to rapidly decrease the radiation in order to decrease the risk to newly dividing cells.

As per Dr. Yaes' review, acute internal contamination of >6 Gy is considered to be lethal and are not apt to respond to supportive medical care. Between doses of 2 to < 6Gy, patients will have acute clinical toxicity of bone marrow suppression, neurologic and gastrointestinal complications that range from mild leukopenia, nausea-vomiting, and headache to marrow suppressive, cognitive impairment and gastrointestinal bleeding. At exposures of 1-2 Gy, the primary risk is delayed cancer development. Therefore, for patients with sublethal exposure in the range of 1-6 Gy, treatment should be aggressive to reduce the exposure to less than 1 Gy. Dr. Yaes recommended 3 gm TID and I agree.

If the exposure is less than 1 Gy, Dr. Yaes' review contained a simulation discussion that recommends treatment for 2-3 half-lives. However, data are lacking to correlate the remaining exposure with the absolute risk of late cancer development. Additionally, in emergency situations and other settings, it may not be possible to determine the effective half-life. The REAC/TS approach has been to treat until radiation is no longer detectable in the feces. Although it could be argued that the correlation of cancer development at low levels is not known, this approach is the most conservative. Therefore, until additional data are available, patients should be treated until radiation is eliminated from the feces.

Additionally, it is conceivable that the rate of fecal elimination and the patient tolerance can be used to individualize the dose. Such individualization would be possible in a controlled setting where radiation counting technology is available.

Pediatrics: Dr. Sancho's review notes that based on modeling, in pediatric patients aged 7-12, the biologic $t_{1/2}$ of ^{137}Cs is similar to adults. Also, in pediatric patients aged one to five years, the $t_{1/2}$ was twice that of adults. Dr. Yaes' review, however, discussed data from actual pediatric patients in Goiania. This revealed a different result from that

predicted by the modeling. Specifically, although during PB treatment, biologic half-life was the same in pediatric and adult patients, off PB the biologic half-life in pediatric patients was shorter than in adults. (See table 2 above). Young pediatric patients may have more rapid cell turnover. Hence, the clinical implication of a shorter half-life is not known.

Overall, 27 pediatric patients received PB in the range of 1 – 3 grams TID. In these patients, PB treatment reduced the whole body half-life of ^{137}Cs by 46% in adolescents and by 43% in children age 4-12 years.

Dr. Sancho's review includes a body weight adjustment analysis shown in the pediatric patients that received 1 gram TID, the dose ranged from 0.32 gram/kg in the 12 year old patient (10 gm PB daily dose, 31 kg weight) to 0.21 gram/kg in the 4 year old patient (3 gm PB daily dose, 14 kg weight).

Dosing experience in pediatric patients under 4 years is not known. However, based on personal communication³, pediatric patients aged 2 to <4 are expected to have biliary and gastrointestinal function that is comparable to a 4 year old. Such patients could be dosed in a manner similar to 4 year patients.

In neonates and infants, there are variations in the developmental maturity of the biliary system and gastrointestinal tract of pre-natal, neo-natal, and infants (0-2). It is not known how these differences will affect the enterohepatic recirculation of cesium or thallium; hence, the ability of Prussian blue to capture these contaminants to increase their fecal elimination. Also, the dose related adverse effects of Prussian blue on an immature gastrointestinal tract are not known. Dose recommendations in this age range would be speculative.

Patients with swallowing difficulties: Stability studies indicate that PB can be adequately mixed in food. On a practical basis, the dose should be titrated to gastrointestinal tolerance. Also, if elimination counts are available, the dose could be titrated to the optimal elimination rate.

Reproductivity and Pregnancy:

Women: Experience with the use of PB in pregnant patients is very limited. One patient with higher exposure (300 mBq) became pregnant 3 years after treatment with PB. At delivery the mother's ^{137}Cs level was substantially higher than that of the baby. The baby was healthy. This shows that cesium can cross the placenta and suggested a protective benefit to the fetus.

Thallium does cross the placenta and has been reported with birth defects and fetal

³ Dr. Hugo Gallo-Torres, Medical Team Leader and Pediatrician, Division of Gastrointestinal Drug Products, CDER, FDA.

death⁴. This article discussed exposure in first, second and third trimester and concluded that the risk appeared to increase with exposure. However, definitive relationship could not be determined.

Since PB is not absorbed, it should not effect the fetus. Thus, treatment with PB should be safe. The labeling carries a category C rating because studies have not been conducted.

Men: As per Dr. Yaes' review, in all men who received > 1 Gy ¹³⁷Cs, long term follow-up revealed that all had either oligospermia or azospermia. (Note: As per Dr. Yaes, the actual number of males that received > 1 Gy can not be determined from the articles.)

Nursing Mothers: Cs is excreted in breast milk. Treatment with PB will decrease radiation exposure to a nursing infant. Although formal studies of the excretion of PB in breast milk were not identified in the literature, PB itself is not absorbed and, therefore, is not expected to be present in breast milk.

Thallium is excreted in the breast milk⁵.

ASSESSMENT

Contamination with radioactive cesium, depending upon the dose, can be acutely lethal, associated with severe morbidity, or associated with the development of delayed radiation associated malignancy. Thallium may be either acutely fatal or may be associated with chronic neurologic, dermatologic and other severe morbidity. The rapid elimination of cesium and thallium is accepted as a surrogate for the decreased risk of toxicity. Because of the severity of the clinical outcomes related to contamination, it is not possible to conduct traditional, controlled clinical trials with long term clinical outcomes. Therefore, it is acceptable to rely on comprehensive epidemiology literature reports of the decontamination response rates. Most specifically, the epidemiologic studies that investigated the relationship of the benefits of Prussian Blue in the decontamination of patients exposed in the Gioania ¹³⁷Cesium accident are the most compelling. These data, along with reliable animal data that show dose response relationships in decreasing the amount of contamination, are considered acceptable to establish the safety and efficacy of PB. The labeled indication should be "for acute and chronic use in patients with known or suspected contamination with radioactive and non-radioactive cesium or thallium to increase their rate of decontamination".

In approving PB, there are some uncertainties. Specifically, the dosing recommendations are based largely on experience, the knowledge of enterohepatic circulation, adverse events, expected body size relationships in pediatrics, and the need to rapidly decontaminate patients while ensuring patient compliance. Specific data to establish linear contamination and PB dose requirements are not available.

⁴ Hoffman, RS, "Thallium Poisoning During Pregnancy: A Case Report and Comprehensive Literature Review", J Toxicology-clinical Toxicology, 2000: 38(7), 767-775.

⁵ IBID.

Likewise, the radiation principles that are included in the package insert, reflect commonly accepted emergency medicine approaches. They have not been tested in controlled clinical trials.

Radiologic emergencies may expose patients to contaminants from elements other than Cesium and thallium. Although hypothetical binding can be predicted, additional animal and, or in vitro studies are needed to evaluate the benefit in other radioactive elements.

Because of the data limitations, additional post approval data should be provided as follows:

1. Epidemiologic, longitudinal follow-up of patients treated with PB is needed to assist in determining how long patients should be treated. These data should be in the form of a patient registry that follows patients for life. This registry should be maintained and analyzed by the NDA holder.
2. Dose adjustment optimization methods should be developed to relate the rate of contaminant elimination with the administered dose. These should consider the amount of contaminant that can be bound per PB dose and the effects of GI transit time.
3. Dose adjustment methods are needed for pediatric patients from neonates to 2 years. These studies should consider biliary maturity, mucosal absorptive maturity, GI surface correlation with weight
4. _____
5. _____

ACTION: Anticipate approval of safety and efficacy database after demonstration of adequate chemistry, manufacturing controls and sterility assurance.

Post approval commitments as itemized above. These may and should begin as soon as possible before approval.

/s/

Patricia Y. Love, MD, MBA

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Patricia Stewart
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CSO
signed by Dr. Patricia Love 11-26-02

Division Director Memorandum

NDA: 21626
DRUG: Prussian blue (Radiogardase)
ROUTE: Oral capsule, 500mg
CLASS: Radioeliminator
CATEGORY: 1P
INDICATION: Radiocesium and thallium decorporation
SPONSOR: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
SUBMITTED: March 10, 2003
COMPLETED: September 29, 2003

RELATED DRUGS: Calcium DTPA
Zinc DTPA

RELATED REVIEWS: (under IND 51700)

Office Director Memo:	Florence Houn
Division Director Memo:	Patricia Love
Chemistry:	Eldon Leutzinger
Clinical:	Robert Yaes
Clinical Pharmacology	Alfredo Sancho
Microbiology:	David Hussong
Pharmacology/Toxicology:	Adebayo Laniyonu
Project Manager:	Lynn Panholzer

BACKGROUND:

Prussian blue is an insoluble blue powder of ferric hexacyanoferrate that is used for cesium-137 and thallium decorporation therapy. Prussian blue is not considered a radioprotectant, as it does not protect the body from the effects of radiation, but rather, it is a radioeliminator. Prussian blue binds to cesium-137 or thallium in the gut thereby interrupting the entero-hepatic circulation and thus increasing the rate of elimination of these elements from the body. The increase in the rate of elimination is considered meaningful as it is expected to result in the reduction of toxicity related to the presence of these elements. Prussian blue has been used under IND for several years to treat people involved in nuclear reactor accidents (cesium-137) and those exposed to rat poison (non-radioactive thallium).

The Agency's finding of the safety and efficacy of Prussian blue (based primarily on published reports from the Goiânia, Brazil incident of 1987)¹ when produced under conditions specified in approved drug applications was published in the Federal Register (FR) Notice of February 4, 2003 (Docket No. 03D-0023). The FR notice also encouraged submission of new drug applications (NDA) for Prussian blue drug products.

¹ See Dr. Yaes' reviewed dated September 16, 2002 for details.

On March 10, 2003, Heyl submitted an NDA for Prussian blue in which they referenced the FR notice thus obviating the submission of clinical, pharmacology-toxicology and clinical pharmacology data. Heyl is the same company that supplied Prussian blue for the treatment of subjects exposed to cesium-137 in the Goiânia, Brazil incident.

CHEMISTRY:

Prussian blue drug substance is a crystalline blue powder of varying granularity (fine to coarse grain). The drug product consists of a hard gelatin capsule containing 500 mg of insoluble Prussian blue and 0-38mg of microcrystalline cellulose. The drug product can vary in appearance from uniformly fine, dark granules to coarse light and dark colored granules. Prussian blue binds cesium and thallium with high affinity by the following mechanisms; ion-exchange, adsorption and mechanical trapping within the crystal structure. Prussian blue drug substance and product are known to be very stable. Cesium binding capacities for the drug product² manufactured in 1987 and currently manufactured product were obtained. The results indicate that the cesium binding kinetics were similar between these batches.

At extreme pH conditions (acid and basic), free cyanide dissociates from Prussian blue. The Sponsor provided dissociation data for current batches, as well as, for a batch manufactured in 1987. The greatest dissociation was seen at low pH values (0-1). In addition, the Sponsor submitted samples to the Division of Product Quality and Research (DPQR) laboratories for FDA testing. The FDA laboratory tested a range of physiologic pH values at specific dwell times³. The intent of the testing was to determine what levels of free cyanide were released under physiologic conditions of therapeutic use. Since the greatest dissociation was seen at low pH values, there was concern that patients with disorders of hypersecretory states (e.g. Zollinger-Ellison Syndrome) may be at risk for cyanide poisoning. To that end, the reviewing pharmacologists, Y. Ouyang and T. Kokate, did an analysis of the data to assess the risk associated with the free cyanide levels found to dissociate at these extreme conditions of pH⁴. The resultant free cyanide levels were compared to the Environmental Protection Agency's reference dose⁵ (RfD) for life time oral exposure to cyanide and to the identified No Observable Adverse Effect Level (NOAEL) in rats. When compared to the RfD the levels expected for the administration of a daily dose of Prussian blue (based on in vitro testing) under simulated physiologic conditions are 1 and 1.9 times higher than the RfD for adults and children, respectively. The RfD is, however, considered to be a conservative estimate as it reflects daily ingestion over a lifetime and therefore, is not reflective of the expected therapeutic duration of use of Prussian blue. When compared to the NOAEL in rat, the levels are 83 and 66 times less than the NOAEL for adults and children, respectively.

² Actual batch used in Goiânia, Brazil was not available for testing. A batch manufactured in the same year with the same manufacturing process was tested.

³ See Dr. He's consultative reviews dated May 28 and August 7, 2003.

⁴ Please see the Pharmacology joint review dated September 29, 2003 for further details.

⁵ The reference dose is 0.02 µg/kg/day. This dose is an estimate of a daily oral exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime.

In addition, the levels of cyanide released from therapeutic doses of Prussian blue is found to be well below the lethal amounts in cases of accidental or intentional poisoning as reported by the Agency for Toxic Substances and Disease Registry. Given these findings and the fact that under IND use, there have been no cases of cyanide poisoning, the reviewing pharmacologists concluded that the free cyanide levels generated from in vitro testing did not pose a significant risk to require a warning in the label.

CONCLUSIONS:

Prussian blue's efficacy is a function of its ability to bind cesium and thallium. By binding to cesium and thallium in the gut, Prussian blue interrupts the entero-hepatic circulation thereby increasing the rate of elimination of these elements. Since prospective trials have not been performed and are not ethical, we are relying on the comparability of cesium binding data for the drug produced in 1987 and that manufactured today to establish the applicability of the efficacy findings in the FR notice to this application. The comparability of the cesium binding data has been confirmed. The Office of Compliance has confirmed the acceptability of the manufacturer's plant inspection.

The safety of Prussian blue for the treatment of cesium and thallium exposure has been established (See FR notice) and no new information was reported in the Sponsor's safety update. However, with each manufacturer, appropriate cyanide dissociation release specifications must be established. The specifications proposed in the NDA are considered adequate. Thus, if Prussian blue is manufactured according to the cyanide dissociation release specifications and dosed according to the label, the risk of cyanide poisoning in the general population is considered negligible.

RECOMMENDATION:

There is adequate evidence to support the approval of Prussian blue for its use for the 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. In addition, the following Phase 4 commitments are recommended:

1. Longitudinal studies involving follow-up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
2. Develop an appropriate dosage form for use in young children.
3. Studies to determine dosing for neonates to 2 years of age (based on human extrapolation and/or animal models).

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revised draft labeling
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the review.

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/s/

Sally Loewke
10/2/03 09:58:46 AM
MEDICAL OFFICER

MEMORANDUM

To: NDA 21,626, Prussian blue

From: Yanli Ouyang and Tushar Kokate, Pharmacologists

Through: Adebayo Lanionu, Supervisory Pharmacologist

Date: October 2, 2003

Re: Prussian blue: Free cyanide release levels in batches from various suppliers (Heyl, Degussa and LCA)

This memo describes the safety assessment of free cyanide levels dissociated from Prussian blue (Pb). The following are our conclusions regarding the amounts of cyanide dissociated from Pb:

- Free cyanide levels obtained from *in vitro* FDA lab experiments at different pHs and dwell times (Appendix 1) are acceptable.
- Although missing data points, it is unlikely that the other batches including the 1987 batch would have higher values.
- No need for cyanide toxicity warning in the label because the amount of cyanide that could be released in acidic or basic conditions in the body, based on the recommended dose of Pb, is acceptable given benefits of the drug.

The highest level of free cyanide detected was 422 µg/g Pb at pH 1 after 24-hour dwell time (See Appendix 1 for details). The corresponding total free cyanide levels in a daily dose of Pb (9 g for adults, 3 g for children) will be as follows

Adults:	3.80 mg/day
Children:	1.27 mg/day

Our assessment of the safety of the cyanide level was based on the EPA's reference dose (RfD) for life time oral exposure of cyanide, which is 20 µg/kg/day (1.0 mg/day for a 50 kg person and 0.18 mg/day for a 9 kg child), and the identified No Observable Adverse effect Level (NOAEL) of 10.8 mg/kg/day in rat after chronic 2-year dietary exposure (see Appendix 2 for details).

The aforementioned maximal daily intake of cyanide resulting from dissociation from Pb is 3.8-fold RfD for adults and 7-fold RfD for children, but 23 and 19 times less than the NOAEL (for adults and children based on body surface area respectively). The RfD is considered conservative from a population safety standpoint as it reflects daily ingestion over a lifetime, and this dose may not be representative of the expected therapeutic duration (30 days or longer of use of Pb).

We believe that gastric (acidic pH) exposure to Pb would be close to 4 hours and intestinal (basic pH) exposure in the range of 1 day. At pH 1 and 4 hour dwell time, the corresponding value of cyanide is even less concerning because it is only 1 and 1.9 folds RfD but 83 and 66 times less than the NOAEL for adults and children respectively.

An average fatal dose of 106 mg cyanide for adult humans has been calculated from case report studies of intentional or accidental poisonings by Environmental Protection Agency. The lowest fatal oral cyanide dose reported in adult humans is 39 mg. However, results of oral intoxication with cyanide must be interpreted with caution because the presence of food in the digestive tract may retard absorption.

FDA lab *in vitro* results has not been collaborated with *in vivo* cyanide release and the true meaning and relevance of our lab values are not known. However, there have been no cases of cyanide poisoning associated with the therapeutic administration of Pb in the IND or literature.

Taken together, we conclude that free cyanide levels dissociated from Pb are acceptable especially considering the risk/benefit approach commonly used in drug safety assessment.

We therefore recommend removing label warning.

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Appendix 1:

Appendix 1 summarizes the free cyanide levels (1, 4, and 24 hour Dwell Time at pH 1 and 9) and calculated daily cyanide intakes resulted from Pb administration.

Supplier (Lab conducting the test)	Batch #	Free cyanide (µg/g Pb) at pH 1 (cyanide intake, mg/day)*			Free cyanide (µg/g Pb) at pH 9 (cyanide intake, mg/day)*		
		Dwell Times			Dwell Times		
		1-hour	4-hour	24-hour	1-hour	4-hour	24-hour
DP-HEYL-ORISE (FDA Lab)	018033	50.2 (A:0.45 C:0.15)	117.6 (A:1.06 C:0.35)	422.0 (A:3.80 C:1.27)	13.7 (A:0.12 C:0.04)	23.4 (A:0.21 C:0.07)	52.0 (A:0.47 C:0.16)
DP-HEYL-ORISE (FDA Lab)	020053	52.2 (A:0.47 C:0.16)	126.9 (A:1.14 C:0.38)	285.8 (A:2.57 C:0.86)	13.7 (A:0.12 C:0.04)	42.5 (A:0.38 C:0.13)	55.7 (A:0.50 C:0.17)
HEYL-API (manufactured in 1987) (FDA Lab)	8712532	33.9 (A:0.31 C:0.10)	95.1 (A:0.86 C:0.29)	303.5 (A:2.73 C:0.91)	---	---	---
HEYL (manufactured in 1987) (Sponsor Lab)	8712532	9.1 (A:0.08 C:0.03)	----	----	---	---	---
	0726M0205	15.4 (A:0.14 C:0.05)	----	----	---	---	---
	0719N0104	24.1 (A:0.22 C:0.07)	51.5 (A:0.47 C:0.15)	----	---	---	---
	Not Listed	45.1 (A:0.41 C:0.14)	84.4 (A:0.76 C:0.25)	----	---	---	---
	Not Listed	4.5 (A:0.04 C:0.01)	8.6 (A:0.08 C:0.03)	----	---	---	---

* Pb: Prussian blue; A: adult; C: child; the numbers inside the () indicated calculated daily cyanide intakes (mg) resulted from Pb administration calculated as daily dose of 9g Pb for adult and 3g for child.

Appendix 2:

RfD of Cyanide for Prussian blue

	RfD (mg/day)	Intended clinical dose (g/day)	Mg Cyanide/g Prussian Blue	ppm*
Adult (50 kg)	1.0	9	0.110	110
Child (9 kg)	0.18	3	0.060	60

* If the free cyanide concentration is below the indicated level the cyanide intake due to administration of Prussian blue will be below the RfD level.

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/s/

Yanli Ouyang
10/2/03 10:19:45 AM
PHARMACOLOGIST

Tushar Kokate
10/2/03 10:21:25 AM
PHARMACOLOGIST

Adebayo Laniyonu
10/2/03 10:29:03 AM
PHARMACOLOGIST
I concur with Drs. Ouyang and Kokate findings and
recommedations.

NDA: 21-626
Product: Radiogardase (insoluble Prussian blue) 0.5gm capsules
Date: September 25, 2003

We refer to your March 10, 2003 new drug application (NDA) for Radiogardase (insoluble Prussian blue), and to our September 22, 2003 request via facsimile for your commitment to perform Phase 4 studies. Please see the additional details below:

1. Longitudinal studies involving follow-up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
 - a. Protocol submission: Within X months of the date of the action letter
 - b. Study start (i.e. the date the database will be ready to accept patient data, should it be necessary): Within Y months of agreement to the protocol
 - c. Annual reports of ongoing study beginning one year from study initiation

2. Pediatric studies
 - a. Develop appropriate dosage form for use in younger children.
 - i. Submission of plan to develop pediatric formulation:
Within X months of the date of the action letter
 - ii. Begin development: Within Y months of agreement to plan
 - iii. Completion of formulation development:
Within Z months of initiation of development

 - b. Studies to determine dosing for neonates to 2 years of age (based on human extrapolation and/or animal models).
 - i. Protocol submission: Within X months of the date of the action letter
 - ii. Study start: Within Y months of agreement to the protocol
 - iii. Final study report submission:
Within Z months of initiation of the study

Please submit a letter stating your commitment to perform these studies and providing your expected timeframes for compliance with each of the tasks listed by September 29, 2003.

If you have any questions, call Lynn Panholzer, Pharm.D., Regulatory Project Manager, at 301-827-3132.

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/s/

Lynn Panholzer .
9/25/03 04:20:11 PM
CSO

To: Florence Houn
Director ODE III

From: John Leighton
Associate Director for Pharmacology/Toxicology, ODE III

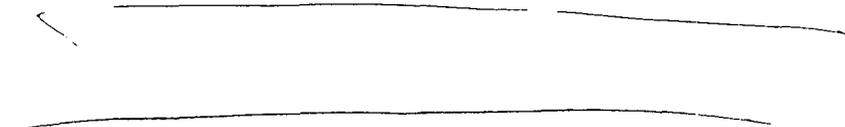
Subject: Radiogardase-Cs (Insoluble Prussian Blue)

Date: September 23, 2002

Introduction

Radiogardase-Cs, also known as Prussian Blue (PB), is used to interrupt the entero-enteric circulation of cesium and thallium, thus enhancing elimination and reducing the body burden of these heavy metals. A draft label is provided for review. No NDA has been filed for this compound.

Review of Pharmacology/Toxicology Safety Issues



However, no outstanding pharmacology issues were identified in the review of PB.

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/s/

Patricia Stewart

10/1/03 06:04:01 PM

CSO

signed originally by John Leighton, Ph.D. on 9-23-2002



NDA: 21-626
Product: Radiogardase (insoluble Prussian blue) capsules 0.5 gm
Date: September 22, 2003

Please refer to your March 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radiogardase (insoluble Prussian blue).

The Food and Drug Administration has determined that the following post-approval (Phase 4) studies are necessary:

1. Longitudinal studies involving follow up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
2. Pediatric studies to develop appropriate dosage form for use in younger children and propose studies to determine dosing for neonates to 2 years of age.

Please submit a letter stating your commitment to perform these studies by September 25, 2003.

If you have any questions, call Lynn Panholzer, Pharm.D., Regulatory Project Manager, at 301-827-3132.

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/s/

Lynn Panholzer :
9/22/03 04:26:20 PM
CSO



NDA: 21-626
Product: Radiogardase (insoluble Prussian blue) capsules 0.5 gm
Date: September 16, 2003

Please refer to your August 13, 2003 submission containing draft bottle and outer box labels.

We have reviewed the referenced material and request the following changes to your draft labels (deleted text is marked with a strikethrough, added text is underlined):

Label and Outer Packaging

C

J

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revised draft labeling
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the review.

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/s/

Lynn Panholzer
9/17/03 10:56:07 AM
CSO

MEMORANDUM OF TELECON

DATE: September 25, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (insoluble Prussian blue)

BETWEEN:

Name: Paul Ferrari, Regulatory Consultant, Hyman, Phelps & McNamara, P.C.

Phone: 202-737-7542

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products,
HFD-160

SUBJECT: Timeframes for Phase 4 studies

In facsimiles from the Division dated September 22 and 25, 2003, the Division requested commitments from the applicant to Phase 4 studies. During this telephone conversation, the Division proposed the following timeframes for completion of the items below:

1. Longitudinal studies involving follow-up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.
 - a. Protocol submission: Within ~~—~~months of the date of the action letter
 - b. Study start (i.e. the date the database will be ready to accept patient data, should it be necessary): Within 6 months of agreement to the protocol
 - c. Annual reports of ongoing study beginning one year from study initiation

2. Pediatric studies
 - a. Develop appropriate dosage form for use in younger children.
 - i. Submission of plan to develop pediatric formulation:
Within 6 months of the date of the action letter
 - ii. Begin development: Within 6 months of agreement to plan
 - iii. Completion of formulation development:
Within ~~—~~ months of initiation of development

- b. Studies to determine dosing for neonates to 2 years of age (based on human extrapolation and/or animal models).
 - i. Protocol submission: Within 6 months of the date of the action letter
 - ii. Study start: ; Within 6 months of agreement to the protocol
 - iii. Final study report submission:
Within 12 months of initiation of the study

The Division requested that the applicant commit to these timeframes or propose alternative timeframes for consideration by the Division.

/s/

Lynn Panholzer
Regulatory Project Manager

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Lynn Panholzer :
10/1/03 11:20:58 AM
CSO

**DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG
PRODUCTS**

Pre-Approval Safety Conference

NDA: 21,626

PRODUCT Radiogardase (insoluble Prussian blue)

APPLICANT: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

DATE: September 29, 2003

ATTENDEES: Sally Loewke, M.D., Acting Director, Division of Medical
Imaging and Radiopharmaceutical Drug Products (DMIRDP)
Lanh Green, R.Ph., M.P.H., Team Leader, Division of Drug Risk
Evaluation (DDRE)
Janos Bacsanyi, M.D., Medical Officer, DDRE
Young Moon Choi, Ph.D., Clinical Pharmacology and
Biopharmaceutics Team Leader for DMIRDP, OCPB
Lynn Panholzer, Pharm.D., Regulatory Project Manager, DMIRDP

BACKGROUND: This NDA was submitted March 10, 2003. The product 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, and is classified as a new molecular entity. As such, a pre-approval safety conference is indicated to discuss post-approval safety surveillance and safety issues with regard to labeling for the product. DMIRDP has already determined that the following Phase 4 studies should be conducted by the applicant: (1) Longitudinal studies involving follow-up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness; (2) Pediatric studies to develop appropriate dosage form for use in younger children and to determine dosing for neonates to 2 years of age.

The Medical Officer for DDRE indicated that DMIRDP had already made changes to the applicant's proposed labeling for Radiogardase that addressed potential safety issues, and that DDRE had no additional safety recommendations. It was noted that the case report form (CRF), called a patient treatment data form in DMIRDP's revised package insert, was condensed significantly in the revised labeling as compared to the applicant's proposed labeling. It was also noted that references to the dissociation of Prussian blue at pH<1 with potential cyanide release were removed from the labeling because DMIRDP determined that this was no longer a significant safety risk.

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/s/

Lynn Panholzer
10/2/03 06:55:46 AM

**DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG
PRODUCTS**

INDUSTRY MEETING MINUTES

APPLICATION: NDA 21,626

DRUG: Radiogardase (Prussian blue)

DATE: August 27, 2003

BETWEEN:

Name:

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND:

Name:

Julie Beitz, M.D., Deputy Director, ODE III
Sally Loewke, M.D., Division Director, DMIRDP
Charles Hoiberg, Ph.D., Deputy Director, ONDC
Eric Duffy, Ph.D., Division Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP,
DNDC II
Lynn Panholzer, Pharm.D., Regulatory Project Manager, DMIRDP

Representing: Division of Medical Imaging and Radiopharmaceutical Drug
Products, HFD-160

BACKGROUND/AGENDA: This meeting was requested by the applicant to discuss the Division's decision to extend the regulatory review clock for this NDA by 90 days. The applicant was notified of the decision during a teleconference between the applicant and the Division held August 8, 2003.

The applicant's regulatory consultant began the meeting with the following statements:

- The applicant was under the impression that review of the NDA was nearing completion.
- The applicant is aware that one of two recent batches of Prussian blue sent to REAC/TS was found by an outside laboratory to have a higher level of free cyanide than was reported for batches submitted in the NDA. Heyl contracted an independent

laboratory to perform tests for free cyanide on both of these batches, and the results showed a lower level of free cyanide consistent with levels reported for NDA batches. Heyl will contact EAC/T S regarding this discrepancy and their additional follow-up data.

- The applicant has tried to assist the FDA in doing tests to confirm data submitted by the applicant in the NDA.
- The applicant reported to the regulatory consultant that the Division said it needed an extension of the review clock to allow more time for the FDA to complete the confirmatory tests and review the NDA amendments.

The Division stated that its goal is a first cycle approval of this NDA, which can be achieved through the 90-day extension. The Division referred to amendments that the applicant has said it will submit prior to the current NDA action goal date of September 13, 2003. The Agency stated that if there are major review issues in these amendments, they must be addressed. Hence, the Division cannot promise that it will be able to take an action by the current goal date. If there are no major review issues in the amendments, an action can be taken.

The Division noted that there are still deficiencies in the NDA that would cause the Division to either extend the review clock or take an action of "approvable" if not adequately addressed by the applicant prior to September 13, 2003. The sponsor's regulatory consultant stated that the applicant would prefer a 90-day extension rather than an approvable action if deficiencies remain on the goal date.

The Division listed the following outstanding items needed from the applicant to complete review of the NDA:

- Data linking product manufactured currently with product manufactured in 1987 that was used in the Goiana accident. The applicant's regulatory consultant stated that this data would be provided in the amendment due to be delivered to the Division September 2, 2003.
- Data on the Goiana drug product regarding the amount of water bound in the molecule (water of hydration) and the amount of surface water needs to be provided. The analytical procedure(s) used to measure the water (e.g., Loss on Drying or the Karl Fischer method) need to be identified. This information is necessary in order to express the amount of active moiety that is contained in "500mg" of drug product used in the Goiana accident. This is needed to ensure consistency of dose/efficacy (and not just weight) from batch to batch.
- Cyanide dissociation data at pHs 7 and 9 at 24 and 48 hours. The Division reiterated that it now considers this a major issue, and referred to the August 21, 2003 telephone conversation between Lynn Panholzer, Project Manager, of this Division, and Paul Ferrari, regulatory Consultant for the applicant, during which the applicant was first notified that this was now considered a major issue as opposed to a minor, non-approvability issue as first stated by the Division during the August 8, 2003 teleconference with the applicant. The applicant's regulatory consultant stated that this data would not be provided in the September 2, 2003 amendment. The Division requested that the applicant include the expected submission date of this data in the

September 2, 2003 amendment. The Division stated that this is a safety issue due to the potential for free cyanide release in vivo.

- A more detailed description of the equations used by the applicant to calculate cyanide dissociation, in μg free CN/gram anhydrous PB.
- Send API batch and drug product currently being held from shipment to EAC/TS pending testing by FDA. Send two additional API batches for inter-batch testing.
- Formal submission of the Certificates of Analysis for the 2 recent batches sent to EAC/TS.

The applicant's regulatory consultant stated that he was aware that Prussian blue manufactured by _____ was granted orphan drug status. He expressed concern that _____ may have submitted an NDA for Prussian blue, and that the FDA wanted to extend the review clock for Heyl's Prussian blue in order to "bundle" the two applications so that they are approved at the same time. The Division stated that it doesn't have a "bundle" policy.

The applicant's regulatory consultant was instructed to contact the Division's Project Manager with any questions, problems, or changes in the timeline for amendment submission.

ACTION ITEMS

1. The applicant will provide the information listed above as outstanding items needed from the applicant to complete review of the NDA to the Division by September 5, 2003.
2. The Project Manager will prepare minutes of this meeting and fax them to the applicant by September 12, 2003.

Meeting minutes prepared by Lynn Panholzer, Pharm.D., Project Manager, HFD-1R0.

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/s/

Lynn Panholzer
9/4/03 02:13:17 PM

MEMORANDUM OF TELECON

DATE: September 26, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (insoluble Prussian blue)

BETWEEN:

Name: _____

Phone: 202-737-7542

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products,
HFD-160

SUBJECT: Miscellaneous Issues

During two telephone conversations, the following issues were discussed:

1. The Division revised the package insert (PI) for insoluble Prussian blue to include the following statement in the

- 2.

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/s/

Lynn Panholzer :
9/29/03 11:02:33 AM

MEMORANDUM OF TELECON

APPLICATION: NDA 21,626

DRUG: Radiogardase (insoluble Prussian blue)

DATE: September 11, 2003

BETWEEN:

Name: Eduard Heyl, M.D., Managing Director
Wolfgang Parr, Ph.D., Managing Director
Andreas Kramer, Qualified Chemist & Laboratory Manager
Brigitte Simons-Wirth, Ph.D., Head of Quality Assurance

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
Phone: 202-737-7542

AND:

Name: Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP,
DNDC II
Lynn Panholzer, Pharm.D., Regulatory Project Manager

Representing: Division of Medical Imaging and Radiopharmaceutical Drug
Products, HFD-160

BACKGROUND/AGENDA: During an August 27, 2003 face-to-face meeting with the applicant, the Division had asked the applicant to measure the amount of water present in its Prussian blue drug product in order to determine the amount of active moiety that was contained in "500mg" of drug product used in the Goiania accident. The Division was seeking this information to ensure consistency of dose/efficacy from batch to batch of drug product. During an August 28, 2003 teleconference, the applicant proposed instead to use iron content to standardize the weight of anhydrous Prussian blue per capsule. The Division agreed to this proposal in a teleconference on September 4, 2003. The current teleconference was held to discuss the Division's new proposal for expressing the amount of active ingredient in a capsule of Radiogardase.

The Division referred to its previous agreement to the applicant's proposal that the amount of anhydrous Prussian blue per capsule be expressed in terms of the amount of iron present as a means to standardize the amount of active ingredient per capsule. The

Division also referred to the applicant's specification for cesium binding (— Cs binding capacity per gram drug substance), and requested that the applicant create another specification for mg Cs binding capacity per capsule as a way to standardize the amount of active ingredient in each capsule, instead of using the amount of iron present. Based on the applicant's current specification for Cs binding per gram drug substance, this new specification would be — Cs binding capacity per capsule. The Division also requested the creation of a similar specification for thallium binding capacity per capsule. The applicant agreed to revise the specification sheet for the drug product to include the new specifications and to submit the revised spec sheet to the FDA by September 12, 2003.

Meeting minutes recorded by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Lynn Panholzer :
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CSO

MEMORANDUM OF TELECON

DATE: September 10, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (Prussian blue)

BETWEEN:

Name:

Phone: 202-737-7542

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP, DNDC II
Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products,
HFD-160

SUBJECT: Miscellaneous Issues

The Division contacted the applicant's regulatory consultants to discuss the following issues:

1. The applicant's August 13, 2003 submission of labeling did not include the package insert's case report form (CRF). The consultants clarified that the CRF was inadvertently omitted and confirmed that the CRF submitted on March 10, 2003 should be included as part of the most recently submitted labeling. The consultants agreed to the Division's request to have the applicant submit a statement to this effect.
2. In a September 3, 2003 fax to the applicant, the Division requested a commitment from the applicant to provide several pieces of information. The applicant responded in a September 5, 2003 submission with a "commitment to address, with due diligence, the post-approval items identified by FDA." The consultants agreed to the Division's request to have the applicant submit a revised letter stating that it commits to provide, rather than address, the specified information.
3. The Division stated that the drug product specification for average capsule content weight must be provided in accordance with USP 905 (content uniformity)-it is currently provided according to Ph. Eur. 2.9.5. The consultants agreed to have the applicant submit a modified specification sheet to reflect this.

Lynn Panholzer, Pharm.D.
Regulatory Project Manager

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/s/

Lynn Panholzer
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MEMORANDUM OF TELECON

APPLICATION: NDA 21,626

DRUG: Radiogardase (insoluble Prussian blue)

DATE: September 5, 2003

BETWEEN:

Name: Eduard Heyl, M.D., Managing Director
Wolfgang Parr, Ph.D., Managing Director
Andreas Kramer, Qualified Chemist & Laboratory Manager
Brigitte Simons-Wirth, Ph.D., Head of Quality Assurance
Johann Ruprecht, Ph.D., Head of Scientific Department

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
Phone: 800-216-3907, ID 256695

AND:

Name: Julie Beitz, M.D., Deputy Director, ODE III
Sally Loewke, M.D., Division Director, DMIRDP
Moheb Nasr, Ph.D., Acting Director, ONDC
Charles Hoiberg, Ph.D., Deputy Director, ONDC
Eric Duffy, Ph.D., Division Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP,
DNDC II
Lynn Panholzer, Pharm.D., Regulatory Project Manager
Representing: Division of Medical Imaging and Radiopharmaceutical Drug
Products, HFD-160

BACKGROUND/AGENDA: This meeting was held at the request of the Division of Medical Imaging and Radiopharmaceutical Drug Products, to obtain responses from the applicant to two questions posed to the applicant on September 3, 2003 in a telephone conversation with its regulatory consultants.

After introduction of participants, the Division's questions were discussed.

1. **Batch numbers 18033 and 20053 differ in appearance and cesium binding, but both were made under NDA conditions. Can Heyl explain these differences?**

Discussion: The applicant stated that the manufacturing process produces a drug substance that consists of particles of different sizes. Also, varying amounts of cellulose may be added to adjust weight. Differences in particle size and cellulose content can cause variability in the appearance of different batches. The applicant stated that quality is not affected by the differences in appearance and Cs binding remains within the specified range. The Division requested that the applicant provide the explanation in writing to the FDA, and remarked that a physical description of the capsule contents should be made in the label. The applicant stated that it can describe a range of physical appearances in labeling.

2. **When will Heyl have cyanide dissociation data at pH 7 and 9?**

Discussion: The applicant stated that this data was available and would be provided informally to the Division on the day of this teleconference, and formally the following week. The Division stated that the data needs to be expressed as microgram cyanide per gram iron. The applicant agreed. The Division also requested that the applicant revise the specification sheets for the drug product to express free cyanide and cesium binding in terms of grams of iron. The applicant agreed.



The Division stated that it was extending the user fee goal date for NDA 21,626 by three months due to the submission of major amendments within three months of the original goal date of September 13, 2003, and that a letter of notification would be provided to the applicant by the end of the day. The applicant suggested that the full 3-month period should not be required to complete review of the NDA, and offered September 30, 2003 as a possible completion date. The Division stated that it could not commit to this date, but anticipated that the full three months would not be necessary. The Division agreed with the applicant that future information that the Division may request that is not required for approval will not result in further extension of review time.

ACTION ITEMS:

1. The applicant will submit a written explanation of the differences in appearance of different batches of its Prussian blue.
2. The applicant will submit data for cyanide dissociation at pHs 7 and 9 expressed as microgram cyanide per gram iron by week ending September 12, 2003.
3. The applicant will submit revised specification sheets for the drug product to express free cyanide and cesium binding in terms of grams of iron by week ending September 12, 2003.
4. _____
5. The Division will prepare a letter of notification of the extension of the user fee goal date for NDA 21,626 and fax a courtesy copy to the applicant by close of business September 5, 2003.

Meeting minutes recorded by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

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/s/

Lynn Panholzer
9/29/03 10:42:25 AM

MEMORANDUM OF TELECON

DATE: September 3-4, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (insoluble Prussian blue)

BETWEEN:

Name: _____

Phone: 202-737-7542

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products,
HFD-160

SUBJECT: Division's September 3, 2003 fax to the applicant of Outstanding Issues

This memorandum summarizes several telephone conversations that took place on September 3 and 4, 2003 between _____ Regulatory Consultants for the applicant, and Lynn Panholzer, Project Manager, of this Division, regarding the Division's September 3, 2003 fax to the applicant of Outstanding Issues needed to complete review of the NDA. The regulatory consultants initiated these discussions to obtain clarification on several items in the fax. The items are numbered as in the fax, and excerpts from the fax appear in quotations. Major points of the discussions follow.

Item #1: "Cesium binding data linking product manufactured currently with product manufactured in 1987 that was used in the Goiana accident."

Discussion: The applicant reiterated that no 1987 product used in the Goiana accident is available, and requested that the Division's September 3, 2003 list be changed to reflect that a batch manufactured at about the same time as the product used in Goiana can be used to satisfy this requirement. The Division stated that it accepts the use of a batch manufactured at about the same time and by the same process as the product used in the Goiana accident to generate the needed data.

Item #2: "Data on the Goiana drug product regarding the amount of water present (water of crystallization and surface water), and the method used in its determination. This information is necessary in order to express the amount of active moiety that is contained in "500 mg" of drug