MEMORANDUM OF TELECON

DATE: August 11, 2004

APPLICATION NUMBER: NDA 21-751, Pentetate zinc trisodium injection
NDA 21-749, Pentetate calcium trisodium injection

BETWEEN:

Name:
Hameln Pharmaceuticals gmbh
Arne Brechmann, Regulatory Affairs Manager
Gudrun Bialas, Regulatory Affairs Manager
B&H Consulting Services, Inc.
Elizabeth Dupras, Associate Project Manager
Helen M. Ribbans, President
Phone: 888-476-3762 #470316
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
FDA:
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III (ODE III)
Sally Loewke, M.D., Deputy Director, Division of Medical Imaging and Radiopharmaceutical Drug Products (DMIRDP)
Eric Duffy, Ph.D, Director of New Drug Chemistry II
Maria Walsh, Regulatory Project Manager, ODE III
Patricia A. Stewart, Regulatory Project Manager, DMIRDP

SUBJECT: The teleconference was requested by FDA to discuss changes to the labeling and phase 4 commitments based on comments from the Pediatric's Division and chemistry issues.

DISCUSSION:

The following major issues were discussed:

Chemistry, Manufacturing , and Controls:

- Although Hameln only submitted ____ of stability data, based on the Agency's knowledge of the stability of the Ca and Zn-DTPA products, FDA is willing to accept a tentative expiry of 2 years with a commitment to continue ongoing stability studies in support of the proposed expiry and to withdraw any lots that fall outside the approved product specifications.
- Hameln was informed that products approved in the US are required to register a USAN name which is the equivalent to the European INN. The Pentetate calcium trisodium has a registered USAN name; however, Pentetate zinc trisodium does not have a USAN name and Hameln will need to apply.

Labeling and Phase 4 Commitment Changes:

The DMIRDP consulted with the Pediatric's Division to review the draft labeling and phase 4 commitments to ensure that we would be in compliance with the new pediatric regulations, the Pediatric Research Equity Act (PREA). Lack of data in the pediatric population for the inhalation route has lead to the following changes in the label. The Agency will defer the PK study in the pediatric population that will be needed to add this route of administration to the label for the pediatric population. Noted changes to the Phase 4 commitment to perform PK studies in the adult and pediatric populations were made as these studies may proceed with IRB approval and need not wait until a post-event situation for collection of this data.

Labeling changes:

Pediatric Use section

The safety and effectiveness of Ca-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population for the intravenous route based on the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an intravenous drug that is renally cleared. . The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

Methods of Administration section (2nd paragraph):

In individuals whose internal contamination is only by inhalation within the preceding 24 hours, Ca-DTPA can be administered by nebulized inhalation as an alternative route of administration. Ca-DTPA should be diluted for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, individuals should be encouraged to avoid swallowing any expectorant. Some individuals may experience respiratory adverse events after inhalation therapy. (See **WARNINGS**) The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

Phase 4 Commitments changes:

2. Human pharmacokinetic study in adult and pediatric subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) compared to the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   b. Study start: Within 6 months of agreement to the protocol
   c. Final study report submission: Within 12 months of initiation of the study

The FDA said they would email the proposed changes and, if the changes were satisfactory, Hameln would fax a commitment to the proposed changes.

- Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

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/s/

Patricia Stewart
8/12/04 10:10:09 AM

11 August 2004

NDA 21-751
Pentetate zinc trisodium injection

Phase 4 Commitment

hameln pharmaceuticals gmbh commits to provide FDA the following:

1. Longitudinal studies involving follow up of Patient Treatment Data Forms and placement of data into a registry for periodic analyses related to post-marketing drug safety and uses.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   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. Agree to submit annual reports of ongoing longitudinal study beginning one year from study initiation.

2. Human pharmacokinetic study in adult and pediatric subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) compared to the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   b. Study start: Within 6 months of agreement to the protocol
   c. Final study report submission: Within 12 months of initiation of the study

Elizabeth N. Dupras
B&H Consulting Services, Inc.
US Agent for hameln pharmaceuticals gmbh

11 August 2004

NDA 21-751
Pentetate zinc trisodium injection

Stability Commitment

hameln pharmaceuticals gmbh proposes a tentative expiry date of 24 months for pentetate zinc trisodium injection.

hameln pharmaceuticals gmbh commits to:

1. Continue the ongoing stability studies in support of the proposed expiry dating.

2. Withdraw from the market any commercial batches found to fall outside the approved drug product specification.

Elizabeth N. Dupras
B&H Consulting Services, Inc.
US Agent for hameln pharmaceuticals gmbh

Stewart, Patricia A

From: Walsh, Maria R
Sent: Wednesday, August 11, 2004 8:36 AM
To: Beitz, Julie G; Addy, Rosemary; Stewart, Patricia A
Cc: Kang, Kyong A; Carmouze, Grace N; Duvall Miller, Beth A
Subject: RE: Your PREA question

Rosemary and Beth,

Although companies agree to phase IV commitments, they are not required by law to do them. However, with a pediatric phase IV commitment, such as the case with the PK study for the DTPAs, sponsor are required under PREA to do those. Is that correct? And for tracking purposes, we make a distinction between them, correct?

Maria

-----Original Message-----
From: Beitz, Julie G
Sent: Tuesday, August 10, 2004 3:46 PM
To: Addy, Rosemary; Walsh, Maria R; Stewart, Patricia A
Cc: Kang, Kyong A; Carmouze, Grace N; Duvall Miller, Beth A
Subject: RE: Your PREA question

Yes, the IV doses are extrapolated from adults to peds. We expect that the recommended IV doses will be adequate for nebulized therapy, but we are asking for the phase 4 pk study so that we can better understand how the dose is delivered into the lungs and subsequently into the bloodstream. This information could help write a more informative label for adults and peds down the road.

Julie

-----Original Message-----
From: Addy, Rosemary
Sent: Tuesday, August 10, 2004 3:38 PM
To: Walsh, Maria R; Stewart, Patricia A; Beitz, Julie G
Cc: Kang, Kyong A; Carmouze, Grace N; Duvall Miller, Beth A
Subject: RE: Your PREA question

Maria,

With the IV route, you extrapolated information from adults and it's already in the label, correct? If so, yes, the studies for the IV are complete.

Rosemary

-----Original Message-----
From: Walsh, Maria R
Sent: Tuesday, August 10, 2004 3:35 PM
To: Stewart, Patricia A; Beitz, Julie G
Cc: Kang, Kyong A; Addy, Rosemary; Carmouze, Grace N; Duvall Miller, Beth A
Subject: FW: Your PREA question

Julie,

On the pediatric page, it appears we can say "complete" for the IV route but "defer" for the nebulizer route. Rosemary, is that OK? The Phase IV commitment for the PK study will now be required because we are giving the sponsor a deferral on the nebulizer route.

Maria

-----Original Message-----
From: Addy, Rosemary
Sent: Tuesday, August 10, 2004 3:28 PM
To: Walsh, Maria R

Cc: Duvall Miller, Beth A; Carmouze, Grace N
Subject: Your PREA question

Maria,

Grace and I just discussed your question and we thought it might be best for me to email the answer to your question and cc Beth so she'll know what we're recommending since she tracks the Phase IV commitments.

Grace agreed that you should give the company a deferral on the PK studies in pediatric patients. As I understand it from our conversation, they already have a Phase IV commitment to do the PK studies in adults and peds. However, with the deferral, the pediatric studies will now become a required Phase IV commitment.

I hope this makes sense. If not, please let me know.

Rosemary Addy, M.H.S.
Regulatory Health Project Manager
FDA/CDER
Office of Counterterrorism & Pediatric Drug Development (OCTAP)
301-827-7313
301-827-7738 (fax)

Stewart, Patricia A

From: Roberts, Rosemary
Sent: Tuesday, August 10, 2004 10:29 PM
To: Beitz, Julie G; Loewke, Sally A; Stewart, Patricia A
Cc: Addy, Rosemary; Carmouze, Grace N; Roberts, Rosemary; Houn, Florence; Mathis, Mitchell; Purucker, Mary E
Subject: DTPAs

Julie,

Thanks for your question about how to address PREA for the Ca- and Zn-DTPA NDAs. I have reviewed the 2 phase 4 commitments and the labels for Ca- and Zn-DTPA. In addition, I have spoken with Mitch Mathis who was directly involved in the data reviewed and used as the basis of the Agency's findings of safety and effectiveness for Ca- and Zn-DTPA; with Mary Purucker who has both pulmonary and CT expertise; and with Shirley Murphy, a pediatric pulmonologist and asthma expert.

By reading the labels, it appears that Ca- and Zn DTPA will be approved for use via the IV route and by nebulized inhalation for adults and for the entire pediatric population from birth upward.

The Pediatric Use subsection states that efficacy in the pediatric population is being extrapolated from the established safety and efficacy in the adult population. The basis for extrapolation is the comparability of the pathophysiologic mechanisms. Further, the dose in the pediatric population has been based on body size adjustment for an intravenous drug that is renally excreted.

- The extrapolation of efficacy from adults to the pediatric population based on the comparability of the pathophysiologic mechanisms is acceptable for the intravenous route of administration for Ca- and Zn-DTPA.
- In light of the indicated use for these drugs in a terrorist or acute event, the basis for dosing in the pediatric population seems reasonable.
- However, Ca-DTPA and Zn-DTPA should **not** be recommended for use via the nebulized inhalation route in the pediatric population, because there are no data on the administration of Ca- or Zn-DTPA via the nebulized route in pediatric patients.
- With the nebulized route of administration, one cannot extrapolate the adult efficacy to the pediatric population because of numerous factors such as: the changes in airway size and respiratory rate with age, the particle deposition, and the complexity of the nebulizer-patient interface (mask vs. mouthpiece).
- Further, as the label warns about the possibility of bronchospasm, the safety of the nebulized inhalation route of administration in children with smaller airways and a greater prevalence of asthma may shift the benefit to risk ratio for this means of administration.

With an approval for the **intravenous route** of administration in the pediatric population, the PREA action is pediatric studies completed (based on extrapolation). For the **inhalation route**, the PREA action is deferral with the timing dependent on a post event scenario that allows the pharmacokinetic study in Commitment 2 to be performed.

With respect to the two phase 4 commitments, it should be stated up front that these studies are to be conducted in a **post event** scenario where individuals are exposed to transuranic element contamination secondary to an accident or terrorist event.

Commitment 1 - Pediatric patients exposed secondary to an event should be included in the longitudinal studies involving follow-up of patient treatment data.... It is not clear as written whether pediatric patients are to be included.

Commitment 2 - With respect to the inclusion of the pediatric subjects in the pharmacokinetic study, ethically this can only be performed in the post event exposure scenario. Ca- and Zn-DTPA could not be administered to normal healthy pediatric subjects for the purpose of obtaining pK measurements as there is no direct benefit to the patients in such a study.

If any questions, please call.

RR

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

2 page(s) have been
removed because it
contains
trade secret
and/or
confidential information
that is not disclosable

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date**: August 3, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: Phase 4 commitments for NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

Hameln Pharmaceuticals gmbh
NDAs 21-749 & 21-751
Ca & Zn-DTPA
July 30, 2004

Phase 4 Commitments:

Please provide a written commitment to the following post marketing studies:

1. Longitudinal studies involving follow up of Patient Treatment Data Forms and placement of data into a registry for periodic analyses related to post-marketing drug safety and uses.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   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. Agree to submit annual reports of ongoing longitudinal study beginning one year from study initiation.

2. Human pharmacokinetic study in adult and pediatric subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) compared to the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   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. Final study report submission: Within 12 months of initiation of the study

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/s/

Patricia Stewart
8/3/04 04:40:43 PM

MEMORANDUM

To: NDA 21-749 (Ca-DTPA) and NDA 21-751 (Zn-DTPA)

From: Adebayo Laniyonu, Ph.D. Supervisory Pharmacologist

Date: July 30, 2004

Re: Additional Preclinical Data Supporting Inhalation Route of Administration:

Stather, J. W., Stradling, G. N., Gray, S.A., Moody, J & Hodgson, M. A. (1985): Use of DTPA for increasing the rate of elimination of Plutonium-238 and Americium-241 from rodents after their inhalation as nitrates; Human Toxicol. 4 573-582

This memo provides additional preclinical literature data to support the effectiveness of Ca- or Zn-DTPA administered by inhalation in the treatment of animals internally contaminated with transuranium elements. The study confirmed the ability of both inhaled DTPA compounds to reduce the lung content, and systemic exposure (liver and skeleton) of ^{241}Am and ^{238}Pu compared with untreated contaminated animals.

The study by Smith and co-workers[1] was used in our original preclinical pharmacology review as a basis to support preclinical evidence of effectiveness of both Ca- and Zn-DTPA administered by inhalation route in the treatment of animals internally contaminated with plutonium. While I concurred with the authors' demonstration of the inhalation route as an effective route of administration, the study only evaluated DTPA's effectiveness against ^{238}Pu. The current cited publication by Stather and colleagues provided additional evidence of efficacy for ^{238}Pu and new evidence of efficacy for ^{241}Am.

Rodents contaminated with aerosolized plutonium and americium were treated with Ca-DTPA and Zn-DTPA. The treatment schedule involved inhalation of Ca-DTPA (0.2 μM/kg; X 0.11 MHD) 30 minutes after contamination followed by inhalation of Zn-DTPA (0.2 μM/kg; X 0.11 MHD) at approximately 6 hours, 1, 2, 3, and 6 days, and then twice weekly to day 26 or day 27.

The treatment regimen reduced the lung deposit of plutonium and americium to 1-2% of that in untreated animals. Systemic deposit of plutonium and americium in liver and skeleton was reduced by half. The authors concluded that Ca-DTPA and Zn-DTPA given via inhalation were effective in reducing the lung ^{241}Am and ^{238}Pu content and systemic exposure compared with untreated contaminated animals.

I concur with the study conclusions.

[1] Smith, V. H. Ballou, J. E., Lund, J. E., Dagle, G .E., Ragan, H. A., Busch, R.H. Hackett, P. L. & Williard, D.W. (1976): Aspects of inhaled DTPA toxicity in the rat, hamster and beagle dog and treatment effectiveness for excorporation of plutonium from the rat (In : Diagnosis and treatment of incorporation of radionuclides; Proc. Seminar Vienna, 1975, IAEA).

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/s/

Adebayo Laniyonu
8/3/04 10:51:56 AM
PHARMACOLOGIST

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

48 Number of Pages (including cover sheet) **Date**: July 30, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: Edited labeling and post marketing commitments for NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

Hameln Pharmaceuticals gmbh
NDAs 21-749 & 21-751
Ca & Zn-DTPA
July 30, 2004

Phase 4 Commitments:

Please provide a written commitment to the following post marketing studies:

1. Longitudinal studies involving completion of Patient Treatment Data Forms and adequate follow-up to assess treatment duration, drug effectiveness and safety. A database/registry should be created so that periodic analyses of safety and effectiveness may be conducted.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   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. Agree to submit annual reports of ongoing longitudinal study beginning one year from study initiation.

2. Human pharmacokinetic study in adult and pediatric subjects to compare and evaluate the absorption, distribution and elimination of Ca and Zn DTPA via inhalation using a commonly available jet type nebulizer (FDA approved model to be selected by the sponsor) compared to the intravenous route. Data/information on dose delivered and the particle size distribution obtained from the specified nebulizer shall be provided.
   a. Protocol submission: Within 6 months of the date of final approval of this application
   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. Final study report submission: Within 12 months of initiation of the study

Stewart, Patricia A

From: Dupras, Elizabeth [edupras@bhconsultingservices.com]

Sent: Thursday, July 15, 2004 2:47 PM

To: 'Stewart, Patricia A'

Cc: Dewald, Mathias; 'Brechmann, Arne'; Ribbans, Helen; Rodgers, Stan

Subject: Response to Information Request from the Drug Shortage Team

Hi Pat,

As discussed earlier, attached is the response that hameln provided to the information request from the drug shortage team. It outlines their manufacturing capacity for both Ca-DTPA and Zn-DTPA.

Please feel free to contact me with any further questions.

Best regards,
Beth

Elizabeth N. Dupras
Associate Project Manager
B&H Consulting Services, Inc.
908-704-1691 x223
908-704-1693 (fax)
edupras@bhconsultingservices.com

ADMINISTRATIVE SUMMARY

NDAs: **21-749 and 21-751**
Products: **Pentetate calcium trisodium injection**
Pentetate zinc trisodium injection
Sponsor: **Hameln Pharmaceuticals, gmbh**

NDA 21-749, Pentetate calcium trisodium injection, letter date April 5, 2004 , stamp date April 6, 2004, and NDA 21-751, Pentetate zinc trisodium injection, letter date April 1, 2004, stamp date April 5, 2004, are indicated for the treatment of patients with known or suspected internal contamination with radioactive isotopes of plutonium, americium, and curium to increase their rate of elimination. The NDAs were given priority review status with User fee goal dates of October 5 and 6, 2004. The User fees were not submitted with the applications; therefore, the applications were not accepted for review until orphan drug designation was granted on April 28, 2004. The User fee clock was reset and the new User fee goal date was determined to be October 28, 2004.

The FDA announced in a Federal Register (FR) notice Vol. 68, No. 178/ Monday, September 15, 2003, page 53984, Docket No. 2003D-0399 that it had concluded that Ca and Zn-DTPA, when produced under conditions specified in approved new drug applications (NDAs), can be found to be safe and effective for the treatment of internal contamination with plutonium, americium and curium. In the same FR notice, the FDA encouraged the submission of NDAs for Ca and Zn-DTPA drug products and announced the availability of a guidance for industry entitled "Calcium and Zinc DTPA Drug Products-Submitting a New Drug Application". In accordance with the guidance, the applicant submitted a 505(b)(2) application and cited the FR notice and literature references upon which the FDA relied making the determination of safety and effectiveness listed therein for the clinical and pre-clinical sections of the NDA. Therefore, also in accordance with the guidance, the NDA included chemistry, manufacturing and controls information, labeling, and patent information.

In response to outside comments on the draft labeling published at the time of the FR notice and the emergence of new information, the following changes were incorporated into the package insert: 1) the duration of dose was changed from a "minimum of 30 days" to " depend on the amount of internal contamination and individual response to treatment", 2) the Zn-DTPA added the route of nebulized inhalation, and 3) a warning was added for Ca-DTPA for patients with hemochromatosis and IM injection.

An approval action has been recommended and the Ca and Zn DTPA drug products will be granted 5 year NME exclusivity and 7 year orphan drug exclusivity which will run concurrently.

Patricia A. Stewart, RTN, Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: July 12, 2004

APPLICATION NUMBER: NDA 21-751, Zn-DTPA (pentetate zinc trisodium)
NDA 21-749, Ca-DTPA (pentetate calcium trisodium)

BETWEEN:

Name:
Elizabeth Dupras, Associate Project Manager
B&H Consulting Services, Inc.
Phone: 908-704-1691 X-223
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
Ravindra Kasliwal, Ph.D., Chemistry Reviewer, DNDC II
Patricia A. Stewart, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: To discuss Submission dated June 28, 2004 and additional CMC comments on labeling.

DISCUSSION:

In follow up to a brief teleconference held July 8, 2004 between Elizabeth Dupras and Patricia Stewart where Ms. Dupras was informed that the proprietary name ——— was not acceptable, the Agency was informed that Hameln decided to use the generic names, pentetate calcium trisodium injection and pentetate zinc trisodium injection.

The Storage section of the Ca and Zn-DTPA labeling needs to be modified by deleting the phrase ———

The How Supplied sections need to add the phrase "equivalent of 1000mg".

The addition of the test for ——— stability protocol that was requested in the June 28, 2004 fax was shipped on July 9, 2004.

The information on the ——— for drug product can be found in the June 28, 2004 submission on page 69 of 157.

Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

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/s/

Patricia Stewart
7/15/04 04:38:59 PM
CSO

MEMORANDUM OF TELECON

DATE: July 12, 2004

APPLICATION NUMBER: NDA 21-751, Zn-DTPA (pentetate zinc trisodium)
NDA 21-749, Ca-DTPA (pentetate calcium trisodium)

BETWEEN:

Name:
Elizabeth Dupras, Associate Project Manager
B&H Consulting Services, Inc.
Phone: 908-704-1691 X-223
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
Ravindra Kasliwal, Ph.D., Chemistry Reviewer, DNDC II
Patricia A. Stewart, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: To discuss Submission dated June 28, 2004 and additional CMC comments on labeling.

DISCUSSION:

In follow up to a brief teleconference held July 8, 2004 between Elizabeth Dupras and Patricia Stewart where Ms. Dupras was informed that the proprietary name ——— was not acceptable, the Agency was informed that Hameln decided to use the generic names, pentetate calcium trisodium injection and pentetate zinc trisodium injection.

The Storage section of the Ca and Zn-DTPA labeling needs to be modified by deleting the phrase ———.

The How Supplied sections need to add the phrase "equivalent of 1000mg".

The addition of the test for ——— the stability protocol that was requested in the June 28, 2004 fax was shipped on July 9, 2004.

The information on the ——— for drug product can be found in the June 28, 2004 submission on page 69 of 157.

Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: July 8, 2004

APPLICATION NUMBER: NDA 21-751, Zn-DTPA (pentetate zinc trisodium)
NDA 21-749, Ca-DTPA (pentetate calcium trisodium)

BETWEEN:

Name:
Elizabeth Dupras, Associate Project Manager
B&H Consulting Services, Inc.
Phone: 908-704-1691 X-223
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
Patricia A. Stewart, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: To inform the sponsor that the newly proposed proprietary name, ——— was not acceptable.

DISCUSSION:

Ms. Dupras was informed that the proprietary name ——— was not acceptable because the Agency was concerned that the name was too close to ——and people might mistakenly think that the Ca-DTPA could be used to treat —— contamination.

Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date**: June 28, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: CMC labeling comments for NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

NDA 21-751 and NDA 21-749 (CMC comments)
June 28, 2004

Request for CMC information:

1. We recommend that the test for [redacted] be added to the stability protocol, as this test is intended to confirm the integrity of Zn-DTPA / Ca-DTPA molecule. Provide updated stability protocol. Do you have any osmolality data on stored samples?

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/s/

Patricia Stewart
6/28/04 03:12:56 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 24, 2004

To: Beth Dupras, U.S. Agent	**From:** Lynn Panholzer, Pharm.D. (for Patricia Stewart)
Company: Hameln Pharmaceuticals	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 908-704-1693	**Fax number:** 301-480-6036
Phone number: 908-704-1691 ext. 223	**Phone number:** 301-827-3132

Subject: NDA 21-749 (Ca-DTPA) and NDA 21-751 (Zn-DTPA): Request for chemistry information

Total no. of pages including cover: 3

Comments: Provide the information requested below by 3pm Monday, June 28, 2004. Please fax the information to the Division fax number above, then mail it to the following address: Food and Drug Administration, Center for Drug Evaluation and Research, Division of Medical Imaging and Radiopharmaceutical Drug Products, Attention: Document Room, 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

Document to be mailed: • YES ☑ NO

NDA: 21-749 (Ca-DTPA)
21-751 (Zn-DTPA)
Sponsor: Hameln Pharmaceuticals
Date: June 24, 2004

Request for chemistry information:

1. Provide specific details of the [redacted] method as performed in your company, including the instrument detail, conditions used, system suitability requirements, standards information and the quantitative aspects.

2. Provide specific details of the [redacted] method.

3. Provide updated methods validation package, to include the updated methods, specifications since the original submission.

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/s/

Lynn Panholzer
6/24/04 03:32:42 PM
CSO

MEMORANDUM OF TELECON

DATE: June 18, 2004

APPLICATION NUMBER: NDA 21-751, Zn-DTPA (pentetate zinc trisodium)
NDA 21-749, Ca-DTPA (pentetate calcium trisodium)

BETWEEN:

Name:
Elizabeth Dupras, Associate Project Manager
B&H Consulting Services, Inc.
Phone: 908-704-1691 X-223
Representing: Hameln Pharmaceuticals gmbh

AND

Name:
Ravindra Kasliwal, Ph.D., Chemistry Reviewer, DNDC II
Patricia A. Stewart, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: To discuss the CMC comments faxed to Hameln June 14, 2004 regarding carton and ampoule labeling.

DISCUSSION:

The sponsor expressed concern that the information that was requested to be included on the ampoule and carton label would not fit and be legible on the ampoule label and asked which items were required. The FDA chemist said to include the following items on the ampoule label:

- The trademark and proprietary name
- Lot #
- Expiration date
- Manufacturer name (address not necessary)
- Strength (1000 mg)
- Volume (5 ml)
- NDC #
- "for single use only"
- Claim small vial label exemption and add "see package insert for more information"

The carton label must include **all** the information requested.

The How Supplied section needs to include the statement that "each carton contains 10 single use ampoules"

The chemist also asked for a method validation package for the NDA.

Minutes recorded by Patricia A. Stewart, Regulatory Project Manager

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

/s/

Patricia Stewart
7/13/04 05:31:00 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 17, 2004	**DESIRED COMPLETION DATE:** July 17, 2004	**ODS CONSULTS #:** 04-0173

TO: George Mills, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

THROUGH: Patricia Stewart
Project Manager
HFD-160

PRODUCT NAME: ~~———~~ (Pentetate Calcium Trisodium Injection) 1 g/5 mL **NDA: 21-749**	**NDA SPONSOR:** Hameln Pharmaceuticals

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name ~~———~~ We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

2. DDMAC finds the proprietary name ~~———~~ acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 28, 2004

NDA # 21-749

NAME OF DRUG: ——
(Pentetate Calcium Trisoidum Injection) 1g/5 mL

NDA HOLDER: Hameln Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products, to review the proprietary name ——, regarding potential name confusion with other proprietary and established drug names.

This is the second proprietary name review for this application. DMETS previously reviewed the proprietary name —— and found it unacceptable (see ODS consult 04-0141). Labels and labeling were reviewed at that time.

PRODUCT INFORMATION

—— (pentetate calcium trisodium injection) is indicated for the treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. The recommended dose on the first day is 1 gram loaded intravenously or by inhalation. A maintenance dose on the second day with —— is recommended. —— will be supplied in ampules containing 1 gram per 5 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look-alike to ' ——— to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name ' ——— Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two proprietary names as having the potential for confusion with ——— Additionally, upon independent review, the established name "itraconazole" was identified as having the potential to sound similar to ——— These products are listed in Table 1 (see below), along with the dosage forms and usual dosage.
2. DDMAC did not have concerns about the name ——— with regard to promotional claims.

Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s), and Strength	Usual adult dose*	Other**
———	Pentetate Calcium Trisodium Injection 1 g/5 mL	A single dose of 1 gram intravenously or by inhalation	N/A
Trinalin	Pseudoephedrine and Azatadine Extended-release Tablets 120 mg/1 mg	1 tablet twice daily	LA
Trisoralen	Trioxsalen Tablets 5 mg (no longer manufactured)	20 to 40 mg two to four hours before measured periods of UVA exposure.	LA
Itraconazole (established name)	Itraconazole Capsules 100 mg Injection 10 mg/mL Oral Solution 10 mg/mL	100 mg to 400 mg once daily	SA

* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/main/trademarks.htm

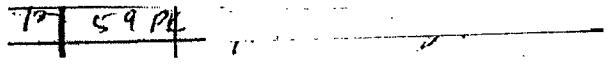
B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the ——— query did not indicate any additional product names that had strong phonetic or orthographic similarities..

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of ——— with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient prescriptions were written for each name, each consisting of a combination of marketed and unapproved drug products and a prescription for ——— (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the inpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient 1 RX: 	Give in clinic today.
Inpatient 2 RX: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S product. The majority of the responses were phonetic/misspelled interpretations of the proposed drug name. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name ' ——— the primary concerns raised were related to potential confusion with the currently marketed products Itraconazole and Trinalin. Although the name Trisoralen was identified as having a potential look-alike similarity to ——— , this name was not reviewed further due to differences in dosage form, strength, usual dose, dosing regimen and the fact that a patients on Trisoralen must be under the supervision of a physician experienced in PUVA (psoralen plus ultraviolet light A) therapy. Although Trisoralen appears in Micromedex and STAT!Ref online databases, it does not appear in the Orange Book, Facts and Comparisons, and 2003 Red Book as it is no longer being manufactured.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that ——— could be confused with the aforementioned names. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of incorrect interpretations from the written and verbal studies were misspelled/phonetic variations of the proposed name, ' ———

1. Itraconazole was thought to sound similar to ' ——— when spoken. Itraconazole is the established name for Sporonox, an antifungal drug product. Itraconazole and ——— owe their sound-alike properties to the similar sounding first and second syllable (it-re) as well as the shared "c" sound at the beginning of the third syllable. Additionally, the names contain five syllables each. The names differ, however, in the last three syllables (con-a-zole vs. ———) which helps to distinguish one name from the other. The products share a similar dosage form (injection), route of administration (intravenous), and dosing regimen (once daily). The products also share a numerically similar strength (10 mg vs. 1 gm) and dose (100 mg vs. 1000 mg). Despite the similarities in product characteristics, DMETS believes that the potential for confusion is minimal due to a lack of convincing sound-alike potential. Additionally, ——— is restricted in use as a counterterrorism drug product.

2 Trinalin was identified as having the potential to look similar to ——— Trinalin contains azatadine and pseudoephedrine and is indicated for use as an antihistamine and decongestant. With exception to the letter ——— Trinalin and ——— share the similarly scripted letters "Trinalin" vs. ——— (see below). Trinalin and ——— differ in dosage form (capsule vs. injection), strength, and dosing regimen (twice daily vs. one time dose). Although the names look somewhat similar, the letter ——— in ' ——— ' will help to distinguish the names from one another while differences in product characteristics will further differentiate the products. Additionally, ——— is restricted in use as a counterterrorism drug product.

——— Trinalin

III. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name ——— We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

B. DDMAC finds the proprietary name ——— acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Alina R. Mahmud, R.Ph.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
7/2/04 09:55:08 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/2/04 10:09:20 AM
DRUG SAFETY OFFICE REVIEWER

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

3 Number of Pages (including cover sheet) **Date**: June 14, 2004

To: Beth Dupras

Fax Number: 908-704-1693 **Voice Number**: 908-704-1691 X-223

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-7496

Message: CMC labeling comments for NDAs 21-749 and 21-751 Ca & Zn-DTPA

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.
THIS DOCUMENT IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

2 page(s) of draft labeling has been removed from this portion of the review.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-749 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: _____
Generic Name: Ca-DTPA (pentetate calcium trisodium injection)
Strengths:

Applicant: Hemeln Pharmaceuticals GmbH

Date of Application: April 5, 2004
Date of Receipt: April 6, 2004
Date clock started after UN:
Date of Filing Meeting: April 22, 2004
Filing Date: June 6, 2004
Action Goal Date (optional): User Fee Goal Date: October 6, 2004

Indication(s) requested: Treatment of internal contamination with plutonium, americium, or curium.

Type of Original NDA: (b)(1) _____ (b)(2) ____X_____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P ____P2_____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___2_____
Other (orphan, OTC, etc.) __orphan_____

User Fee Status: Paid _____ Exempt (orphan, government) ___OPD____
Waived (e.g., small business, public health) __X_____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO
User Fee ID # _____
Clinical data? NO, Referenced to NDA # _FR Vol. 68, No. 178, page 53984_____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO X

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO X

Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO X

- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? YES NO
- Is it an electronic CTD? YES NO X
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO X
- Exclusivity requested? YES, ___7____years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] 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."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: NA

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) __12/10/03_____
  NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES X NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES X NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO

If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES X NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: N/A
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). N/A
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO X
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  __X__ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES X NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    NA YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    NA YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES X NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    N/A IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES X NO

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-751 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: [redacted]
Generic Name: Zn-DTPA (pentetate zinc trisodium injection)
Strengths:

Applicant: Hemeln Pharmaceuticals GmbH

Date of Application: April 1, 2004
Date of Receipt: April 5, 2004
Date clock started after UN:
Date of Filing Meeting:
Filing Date: June 5, 2004
Action Goal Date (optional): User Fee Goal Date: October 5, 2004

Indication(s) requested: Treatment of internal contamination with plutonium, americium, or curium.

Type of Original NDA: (b)(1) _____ (b)(2) ____X_____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P ____P1_____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___1_____
Other (orphan, OTC, etc.) __orphan_____

User Fee Status: Paid _____ Exempt (orphan, government) ___OPD____
Waived (e.g., small business, public health) __X_____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO
User Fee ID # _____
Clinical data? NO, Referenced to NDA # _FR Vol. 68, No. 178, page 53984_____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO X

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO X