CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-749

21-751

CHEMISTRY REVIEW(S)

NDA 21-749

Pentetate Calcium Trisodium Injection

NDA 21-751

Pentetate Zinc Trisodium Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Hameln Pharmaceiuticals, GmbH
Langes Field 13
31789 Hameln, Germany

Indication: Treatment for known or suspected internal contamination with Pu, Am, or Cu to increase the rate of elimination

Presentation: Colorless sealed ampoules, 1 g/5 mL fill

EER Status: Acceptable 22_JUN_2004

Consults: DMETS – Tradename: none
Statistics – none
EA – no consult - waiver requested – granted
Microbiology – acceptable 30-JUN-2004

Phase IV Commitments: No CMC Phase IV Commitments

The original NDA was received 06-APR-2004

The DTPA **drug substances** are manufactured by:

Manufacturing and controls information was reviewed in DMF ~ The DMF is acceptable. The drug substance is USP – complies with USP specifications - acceptable. A re-test period of - years was requested, and is supported by the established -year expiry extant at —. The stability testing protocol is considered adequate.

Conclusion
Drug substance is satisfactory.

The **drug products** are the Ca and Zn complexes of DTPA formed in situ during drug product manufacture.

Manufacturer:

Hameln Pharmaceiuticals, GmbH
Langes Field 13
31789 Hameln, Germany

The Ca or Zn DTPA complexes are formed in situ and pH adjusted to produce isotonic solutions of the drug substances. The manufacturing method is a simple ——— and ampoule sealing operation. Three demonstration batches were produced. Adequate in-process controls are in place. The sterility assurance data package was considered acceptable by the Microbiology staff.

The proposed regulatory specifications are acceptable (including impurities). Very limited stability data were submitted (——— however it is considered sufficient to grant a 2 year tentative expiry. The firm accepted this in a TCon on 8/11/2004. Further, a commitment was made to withdraw any batches falling outside specification. The stability testing protocol is considered adequate. The established name for the Ca complex is USAN, however the Zn complex is not USAN – the firm has agreed (above cited TCon) to obtain a USAN designation.

Labeling is acceptable.

The overall Compliance recommendation is acceptable as of 22-JUN-2004.

Conclusion
Drug product is acceptable.

Overall Conclusion
From a CMC perspective the applications are recommended for approval.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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

/s/

Eric Duffy
8/11/04 11:28:31 AM
CHEMIST

NDA 21-749

Pentetate Calcium Trisodium Injection)

Hameln Pharmaceuticals GmbH.
Langes Field 13
31789 Hameln
Germany

Ravindra K. Kasliwal, Ph.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-749
2. REVIEW #: 1
3. REVIEW DATE: 28-Jun-2004, Revised – 20-Jul-2004
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-Apr-2004
Amendment (BZ)	14-May-2004
Amendment (BC)	11-Jun-2004
Amendment (BL)	17-Jun-2004
Amendment (BZ)	28-Jun-2004
Amendment (BC)	09-Jul-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Hameln Pharmaceuticals GmbH
Address:	Langes Geld 13, 31789 Hameln, GERMANY
Representative:	Helen M Ribbens, B & H Consulting Services Inc. 55 North Gaston Avenue, Somerville NJ 08876
Telephone:	Company: +49-5151-5810 U.S. Agent: (908) 704-1691

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ———— ™ (company does not want to use this in labeling)
b) Non-Proprietary Name (USAN): Pentetate Calcium Trisodium
c) Code Name/# (ONDC only): Ca-DTPA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2) (Referenced to the Federal Register notice, Vol. 68, No. 178, page 53984)

10. PHARMACOL. CATEGORY: Chelating Agent (Internal Radio-decontamination)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1000 mg (200 mg/mL)

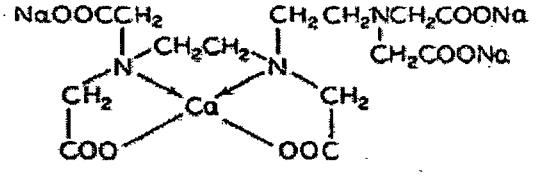
13. ROUTE OF ADMINISTRATION: Intravenous or Inhalation

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



NOTE:	Following information was extracted from USP Dictionary of USAN and International Drug Names:
Molecular Info.	$C_{14}H_{18}CaN_3Na_3O_{10}$; 497.35.
Chemical Name	[Calcium Trisodium Pentetate is INN and BAN.] (1) Calciate(3-), [*N,N*-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]-, trisodium; (2) Trisodium [*N,N*-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]calciate(3-).
CAS Numbers	*CAS-12111-24-9; CAS-67-43-6* [pentetic acid].
Category	*Chelating agent (plutonium).*
Code Designations	*✧NSC-34249*

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
—	II	—	Pentetic acid —	1	Adequate for this NDA	25-Jun-04	Some information is requested to be updated in the DMF

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	N 21-751	Parallel application for Zn-DTPA
IND	—	—
IND	I 4,041	—
Federal Register	Vol. 68, No. 178, pp 53984	FDA's federal register notice asking applicants to apply.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	15-Jul-2004	Office of Compliance
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	Package submitted – FDA method validation pending	28-Jun-2004	Ravindra K. Kasliwal, Ph.D.
ODS	The name — is acceptable by ODS.	02-Jul-2004	Alina R. Mehmud, R.Ph.
EA	Acceptable categorical exclusion claim.	28-Jun-2004	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	02-Jul-2004	Brian Reily, Ph.D.

Reviewer's comment: Although the name is acceptable to ODS, the division had some concerns over the name. Since then the applicant has decided to just go with the established name.

The Chemistry Review for NDA 21-749

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval action for manufacturing and controls under section 505 of the Act. All manufacturing facilities are currently in acceptable GMP compliance. The company should be told that the currently approve expiration dating period for the product is

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no phase 4 commitments recommended from a CMC point of view.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The product contains pentetic acid drug substance which is intended to give, in situ, pentetate calcium trisodium in the finished drug product. The finished drug product is supplied in a colorless 5 mL sealed ampoule as a clear colorless solution. the drug product contains 158.17 mg pentetic acid, 40.24 mg calcium carbonate which are intended to provide an equivalent of 200 mg of pentetate calcium trisodium. Additionally, the drug product also contains NaOH (used for pH adjustment) and of water for injection Each ampoule contains 5 mL total volume as a ready to use product.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rate of elimination. The drug product is intended for intravenous administration either directly as intravenous push over 3-4 minutes (1 gram in 5 ml volume) or by intravenous infusion diluted in 100 – 250 mL of 5% dextrose (D_5W), Ringer's lactate or Normal saline. In patients where the contamination has occurred only through inhalation, the product may be administered through nebulized inhalation (1:1 dilution with saline) as an alternate route of administration. A maximum initial loading dose of 1 gram in indicated, with subsequent maintenance dose of 1.0 gram / day administered intravenously (for pediatric (<12 years)patients a dose of 14 mg/kg is indicated with a maximum dose of 1.0 gram/day). The drug product is to be stored between15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has submitted data to sufficiently demonstrate control over the identity, purity quality of the drug substance and over identity, strength, purity and quality of the finished drug product. The controls to assure quality of the product are acceptable. The facilities have been inspected and have been found to be in acceptable cGMP compliance (EES date 15-Jul-2004).

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Kasliwal/28-Jun-2004/20-Jul-2004
Leutzinger/Date –see electronic review signoff sheet
Stewart/Date – see electronic review sheet

C. CC Block

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

---

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

/s/

Ravi Kasliwal
7/22/04 09:01:16 AM
CHEMIST

Eldon Leutzinger
7/22/04 10:27:04 AM
CHEMIST
I concur with the conclusions and recommendation

CHEMISTRY REVIEW

NDA 21-751

Pentetate Zinc Trisodium Injection

Hameln Pharmaceuticals GmbH.
Langes Field 13
31789 Hameln
Germany

Ravindra K. Kasliwal, Ph.D
DNDC-II, ONDC
Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-751

2. REVIEW #: 1

3. REVIEW DATE: 28-Jun-2004; Revised 20-July-2004

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-Apr-2004
Amendment (BZ)	14-May-2004
Amendment (BC)	11-Jun-2004
Amendment (BZ)	28-Jun-2004
Amendment (BC)	09-Jul-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Hameln Pharmaceuticals GmbH
Address:	Langes Geld 13, 31789 Hameln, GERMANY
Representative:	Helen M Ribbens, B & H Consulting Services Inc. 55 North Gaston Avenue, Somerville NJ 08876
Telephone:	Company: +49-5151-5810 U.S. Agent: (908) 704-1691

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ——— (company does not want to use this in labeling)
b) Non-Proprietary Name (USAN): No USAN name
(FDA assigned name: Pentetate zinc trisodium)
c) Code Name/# (ONDC only): Zn-DTPA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2) (Referenced to the Federal Register notice, Vol. 68, No. 178, page 53984)

10. PHARMACOL. CATEGORY: Chelating Agent (Internal Radio-decontamination)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1000 mg (200 mg/mL)

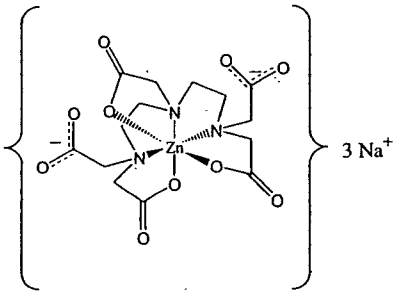
13. ROUTE OF ADMINISTRATION: Intravenous or Inhalation

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: Pentetate Zinc Trisodium
Molecular Formula: $Na_3ZnC_{14}H_{18}N_3O_{10}$
Molecular Weight: 522.7 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	—	Pentetic acid	1	Adequate for this NDA	25-Jun-2004	Some information is requested to be updated in the DMF

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	N 21-749	Parallel application for Ca-DTPA
IND	I 4,041	———
Federal Register	Vol. 68, No. 178, pp 53984	FDAs federal register notice asking applicants to apply.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Acceptable	15-Jul-2004	Office of Compliance
Pharm/Tox	Not applicable		
Biopharm	Not applicable		
LNC	Not applicable		
Methods Validation	Pending	28-Jun-2004	Ravindra K. Kasliwal, Ph.D.
ODS	The Name ——— is acceptable by ODS.*	25-Jun-2004	Alina R. Mehmud, R.Ph.
EA	Acceptable categorical exclusion claim.	28-Jun-2004	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	25-Jun-2004	Brian Reily,Ph.D.

***Reviewer's comment**: Although the name is acceptable to ODS, the clinical division had some concerns over the name. Since then the applicant has decided to just go with the established name.

The Chemistry Review for NDA 21-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval action for manufacturing and controls under section 505 of the Act. All manufacturing facilities are currently in acceptable GMP compliance. The company should be told, in the approval letter, that the currently approve expiration dating period for the product is ———

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no phase 4 commitments recommended from a CMC point of view.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The product contains pentetic acid drug substance which is intended to give, in situ, pentetate zinc trisodium in the finished drug product. The finished drug product is supplied in a colorless 5 mL sealed ampoule as a clear colorless solution. [redacted] the drug product contains 150.51 mg pentetic acid, 31.14 mg zinc oxide ; [redacted] which are intended to provide an equivalent of 200 mg of pentetate zinc trisodium. Additionally, the drug product also contains [redacted] NaOH used for pH adjustment) and [redacted] of water for injection [redacted] Each ampoule contains 5 mL total volume as a ready to use product.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for treatment of patients with known or suspected internal contamination with plutonium, americium, or curium to increase the rate of elimination. The drug product is intended for intravenous administration either directly as intravenous push over 3-4 minutes (1 gram in 5 ml volume) or by intravenous infusion diluted in 100 – 250 mL of 5% dextrose (D_5W), Ringer's lactate or Normal saline. In patients where the contamination has occurred only through inhalation, the product may be administered through nebulized inhalation (1:1 dilution with saline) as an alternate route of administration. A maximum initial loading dose of 1 gram in indicated, with subsequent maintenance dose of 1.0 gram / day administered intravenously (for pediatric (<12 years)patients a dose of 14 mg/kg is indicated with a maximum dose of 1.0 gram/day). The drug product is to be stored between 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has submitted data to sufficiently demonstrate control over the identity, purity quality of the drug substance and over identity, strength, purity and quality of the finished drug product. The controls to assure quality of the product are acceptable. The facilities have been inspected and have been found to be in acceptable cGMP compliance (EES date 15-Jul-2004).

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Kasliwal/28-June 2004/20-Jul-2004
Leutzinger/Date - see electronic review signoff sheet
Stewart/Date - see electronic review sheet

C. CC Block

See electronic review.

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

---

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

/s/

Ravi Kasliwal
7/22/04 08:58:16 AM
CHEMIST

Eldon Leutzinger
7/22/04 01:05:51 PM
CHEMIST
I concur with the conclusions and recommendation

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21749/000	Action Goal:	
Stamp:	06-APR-2004	District Goal:	07-DEC-2004
Regulatory Due:	28-OCT-2004	Brand Name:	[redacted]
Applicant:	HAMELN PHARMS	Estab. Name:	(PENTETATE CALCIUM TRIS
	31789	Generic Name:	CA-DTPA(PENTETATE
	HAMELN, , GM		CALCIUM TRISODIUM INJE
Priority:	P	Dosage Form:	(INJECTION)
Org Code:	160	Strength:	1 G/AMPOULE; 200 MG/ML

Application Comment: THIS IS A COUNTER TERRORISM PRODUCT OF EXTREMELY HIGH IMPORTANCE. HAMELN HAS INDICATED THAT THE FACILITIES WILL BE READY FOR INSPECTION AT THE END OF APRIL 2004. WE REQUEST THAT THE FACILITIES BE INSPECTED SOON THEREAFTER BECAUSE OF THE COUNTER TERRORISM NATURE OF THE PRODUCT. (on 02-MAR-2004 by R. KASLIWAL (HFD-160) 301-827-7494)

Contacts:	R. KASLIWAL	(HFD-160)	301-827-7494	, Review Chemist
	E. LEUTZINGER	(HFD-160)	301-827-7510	, Team Leader

Overall Recommendation: ACCEPTABLE on 15-JUL-2004by S. FERGUSON(HFD-322)301-827-9009

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-MAR-2004				KASLIWALR
SUBMITTED TO DO	02-MAR-2004	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	08-MAR-2004	GMP			ADAMSS
INSPECTION SCHEDULED	07-MAY-2004		16-JUN-2004		ADAMSS
INSPECTION PERFORMED	16-JUN-2004		16-JUN-2004		ADAMSS
RECOMMENDATION	15-JUL-2004			ACCEPTABLE	ADAMSS

INSPECTION

BASED ON REVIEW OF 483 AND INVESTIGATOR'S RECOMMENDATION. AWAITING EIR AND FIR M'S

RESPONSE

OC RECOMMENDATION 15-JUL-2004 ACCEPTABLE
FERGUSONS

DISTRICT RECOMMENDATI
ON

Establishment: CFN 9611057 FEI 3002807877

PHARMA HAMELN GMBH

LANGES FELD 30 - 38

HAMELN, , GM

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21751/000	Action Goal:	
Stamp:	05-APR-2004	District Goal:	04-FEB-2005
Regulatory Due:	28-OCT-2004	Brand Name:	————
Applicant:	PHARMA HAMELN GMBH	Estab. Name:	(PENTETATE ZINC TRISODI
	HAMELN, , GM	Generic Name:	PENTETATE ZINC DISODIUM
	P		
Priority:	160	Dosage Form:	(INJECTION)
Org Code:		Strength:	1 G/AMPOULE; 200 MG/ML

Application Comment: THIS IS A COUNTER TERRORISM PRODUCT OF EXTREMELY HIGH IMPORTANCE. HAMELN HAS INDICATED THAT THE FACILITIES WILL BE READY FOR INSPECTION AT THE END OF APRIL 2004. WE REQUEST THAT THE FACILITIES BE INSPECTED SOON THEREAFTER BECAUSE OF THE IMPORTANT COUNTER TERRORISM NATURE OF THE PRODUCT. (on 02-MAR-2004 by R. KASLIWAL (HFD-160) 301-827-7494)

Contacts:	R. KASLIWAL	(HFD-160)	301-827-7494	, Reviewer Chemist
	E. LEUTZINGER	(HFD-160)	301-827-7510	, Team Leader

Overall Recommendation: ACCEPTABLE on 15-JUL-2004by S. ADAMS (HFD-322)3
01-827-9051

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

lestone Name Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC KASLIWALR	02-MAR-2004			
SUBMITTED TO DO DAMBROGIOJ	02-MAR-2004	GMP		
ASSIGNED INSPECTION T ADAMSS	08-MAR-2004	GMP		
INSPECTION SCHEDULED ADAMSS	07-MAY-2004		16-JUN-2004	
INSPECTION PERFORMED ADAMSS	16-JUN-2004		16-JUN-2004	
DO RECOMMENDATION ADAMSS	15-JUL-2004			ACCEPTABLE

INSPECTION

BASED ON REVIEW OF 483 AND INVESTIGATOR'S RECOMMENDATION. AWAITING EIR AND FIR M'S

RESPONSE.

OC RECOMMENDATION 15-JUL-2004 ACCEPTABLE
ADAMSS

DISTRICT RECOMMENDATI

C

Establishment: CFN 9611057 FEI 3002807877

PHARMA HAMELN GMBH

LANGES FELD 30 - 38

HAMELN, , GM