HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PENTETATE ZINC TRISODIUM INJECTION** safely and effectively.
See full prescribing information for **PENTETATE ZINC TRISODIUM INJECTION.**

Pentetate zinc trisodium injection (Zn-DTPA)

For intravenous or inhalation administration
Initial U.S. Approval: 2004

WARNING: ASTHMA EXACERBATION WITH NEBULIZATION and DEPLETION OF TRACE METALS DURING THERAPY

See full prescribing information for complete boxed warning.

- Nebulized Zn-DTPA may be associated with asthma exacerbation. (5.1)
- Zn-DTPA is associated with depletion of trace metals. The risk for depletion increases when Zn-DTPA is administered over several months. Monitor serum zinc levels, serum creatinine, BUN, electrolytes, urinalysis and blood cell counts during Ca-DTPA or Zn-DTPA therapy. (2.4, 5.2)

----------INDICATIONS AND USAGE----------

Pentetate zinc trisodium injection is a radiomitigation chelator indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination. (1)

----------DOSAGE AND ADMINISTRATION----------

Chelation treatment is most effective if administered within the first 24 hours. Administer Ca-DTPA, if available, as the initial dose. (2.1, 2.2)

If Ca-DTPA is not available during the first 24 hours,

- in adults and adolescents, administer intravenously a single 1.0 gram Zn-DTPA initial dose. (2.1)
- in children less than 12 years of age, administer intravenously a single 14 mg/kg Zn-DTPA initial dose, not to exceed 1.0 grams. (2.1)

After the first 24 hours, continue chelation therapy with Zn-DTPA:

- in adults and adolescents, administer intravenously 1.0 gram Zn-DTPA once daily. (2.1)
- in children less than 12 years of age, administer intravenously 14 mg/kg Zn-DTPA once daily, not to exceed 1.0 gram daily. (2.1)

See Full Prescribing Information for dose (2.1) and nebulized chelation therapy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

1000 mg / 5 mL single-use ampoules. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Nebulized chelation therapy may be associated with exacerbation of asthma. Monitor patients for signs and symptoms of asthma exacerbation when administering Zn-DTPA by the inhalation route. (5.1)
- Zn-DTPA is associated with depletion of endogenous trace metals (e.g., zinc, magnesium, manganese). (5.2)
- Take appropriate safety measures to minimize contamination of care-takers by contaminated body fluids. (5.3)

----------ADVERSE REACTIONS----------

There is limited experience with Zn-DTPA. Nebulized chelation therapy may be associated with exacerbation of asthma. Headache, light headedness, and pelvic pain have been reported. (6)

To report SUSPECTED ADVERSE REACTIONS, contact the hameln Pharmacovigilance Department at +44 (0) 7706 210 133 or drugsafety@hameln.co.uk or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Women with known or suspected internal contamination with radiocontaminants should not breast feed, whether or not they are receiving chelation therapy. (8.3)
- Pediatric Use: Safety and effectiveness of intravenous Zn-DTPA were extrapolated from adults. Safety and effectiveness of nebulized route of administration have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

Zn-DTPA is indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

2 DOSAGE AND ADMINISTRATION

2.1 Dose

Administer Ca-DTPA as the initial dose during the first 24 hours after internal contamination. Ca-DTPA is more effective than Zn-DTPA during this time period (see Ca-DTPA labeling). If Ca-DTPA is not available, use Zn-DTPA as initial therapy. On the next day, if additional chelation therapy is indicated, begin daily treatment with Zn-DTPA. If Zn-DTPA is not available, chelation therapy may continue with Ca-DTPA and concomitant mineral supplements containing zinc should be given (see Ca-DTPA labeling).

Do not administer more than one dose per 24 hour period.

If Ca-DTPA is not available during the first 24 hours:

- in adults and adolescents, administer intravenously a single 1.0 gram initial dose of Zn-DTPA.
- in children less than 12 years of age, administer intravenously a single 14 mg/kg initial dose of Zn-DTPA, not to exceed 1.0 gram.

After the first 24 hours, continue chelation therapy with Zn-DTPA:

- in adults and adolescents, administer intravenously 1.0 gram Zn-DTPA once daily
- in children less than 12 years of age, administer intravenously 14 mg/kg Zn-DTPA once daily, not to exceed 1.0 gram daily.

Renally Impaired Patients

No dose adjustment is needed. However, renal impairment may reduce the rate at which chelates remove radiocontaminants from the body. In heavily contaminated patients with renal impairment, dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public.

2.2 General

Chelation treatment is most effective if administered within the first 24 hours after internal contamination. Start chelation treatment as soon as possible after suspected or known internal contamination. When treatment cannot be started right away, give chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination. The chelating effects of Zn-DTPA are greatest when the radiocontaminants are still circulating or are in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radiocontaminants become sequestered in liver and bone.

If internal contamination with radiocontaminants other than plutonium, americium or curium, or unknown radiocontaminants is suspected, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

2.3 Methods of Administration

Use intravenous administration of Zn-DTPA if the route of internal contamination is not known or if multiple routes of internal contamination are likely. Administer Zn-DTPA solution (1 gram in 5 mL) either with a slow intravenous push over a period of 3-4 minutes or by intravenous infusion over 30 minutes diluted in 100-250 mL of 5% dextrose in water (D5W), Ringer's Lactate, or Normal Saline.

In individuals whose internal contamination is only by inhalation, Zn-DTPA can be administered by nebulized inhalation as an alternative route of administration. Dilute Zn-DTPA for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, encourage patients to avoid swallowing any expectorant. Some individuals may experience respiratory adverse events after inhalation therapy. *[See Warnings and Precautions (5.1)]* The safety and effectiveness of the nebu-

During Treatment

- Measure the radioactivity in blood, urine, and fecal samples weekly to monitor the radioactive contaminant elimination rate.
- Monitor CBC with differential, BUN, serum creatinine and electrolytes, and urinalysis measurements.
- Record any adverse events from Zn-DTPA.

3 DOSAGE FORMS AND STRENGTHS

1000 mg / 5 mL single-use ampoules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma Exacerbation

Nebulized chelation therapy is associated with asthma exacerbation. Monitor patients for signs and symptoms of asthma exacerbation when administering Zn-DTPA by the inhalation route. *[See Adverse Reactions (6)]*

5.2 Depletion of Body Trace Mineral Stores

Zn-DTPA treatment may lead to depletion of body stores of endogenous metals (e.g. magnesium, manganese). The risk for depletion increases when Zn-DTPA is administered over several months. Monitor serum zinc levels, electrolytes and blood cell counts during Ca-DTPA or Zn-DTPA therapy. Give mineral or vitamin plus mineral supplements as appropriate. *[See Dosage and Administration (2.4)]*

5.3 Risks to Care-takers

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with plutonium, americium, or curium, Zn-DTPA treatment increases excretion of radioactivity in the urine. Take appropriate safety measures to minimize contamination of others. *[See Patient Counseling Information (17)]*

6 ADVERSE REACTIONS

In the U.S. Registry, a total of 646 individuals received at least one dose of either Ca-DTPA or Zn-DTPA. Of these, 82 received Zn-DTPA by one or more routes of administration. Forty-eight individuals were dosed by intravenous administration, 18 by inhalation and 8 by other or unknown routes of administration.

Of the individuals that received Zn-DTPA, 23/62 (37%) received one dose and 8 (13%) received two doses. The remaining 31 individuals received three or more doses. The largest number of Zn-DTPA doses to a single individual was 574 doses delivered over 3.6 years.

Overall, the presence or absence of adverse events was recorded in 310/646 individuals. Of these 19 (6.1%) individuals reported at least one adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 1 individual treated with Zn-DTPA reported headache, lightheadedness, and pelvic pain.

Two individuals experienced cough and/or wheezing with nebulized Ca-DTPA therapy however there was no report of such events with nebulized Zn-DTPA.

7 DRUG INTERACTIONS

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. When an individual is contaminated with multiple radiocontaminants, or when the radiocontaminants are unknown, additional therapies may be needed (e.g., Prussian blue, potassium iodide).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

There are no adequate and well-controlled studies of Zn-DTPA use in pregnant

Questions and Answers on Calcium-DTPA and Zinc-DTPA (Updated)

Bioterrorism and Drug Preparedness

- Products Approved for Anthrax
- Products Approved for Other Bioterrorism Emergencies
- Radiation Emergencies
- Products Approved for Chemical Emergencies
- Pediatric Medical Countermeasures | Drugs

Content current as of:
01/09/2015

1. What is the Food and Drug Administration (FDA) announcing today?

The FDA is announcing its decision to approve Hameln's new drug applications (NDAs) for pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) for the treatment of internal contamination with plutonium, americium, or curium to increase the rates of elimination of these materials from the body.

This is part of FDA's continuing efforts to foster the development and availability of drug products for treatment of people who are accidentally contaminated internally with radioactive materials (i.e., radioactive material that gets inside the body), and as countermeasures to terrorist attacks. Contamination with radioactive materials could occur from laboratory or industrial accidents, or through terrorist attacks. Radioactive materials could be spread through an explosion of a radiation dispersal device (RDD), commonly known as a "dirty bomb." A dirty bomb is a conventional explosive device that contains radioactive material. Radioactive materials could also be spread through use of an improvised nuclear device from which only a small portion of the plutonium is consumed in the nuclear reaction and the rest of the plutonium is spread through the air by the explosion.

2. What are Ca-DTPA and Zn-DTPA?

research
development
supply chain

hameln rds

CERTIFICATE OF ANALYSIS

Name of API : **$ZnNa_3DTPA$**
Diethylenetriaminepentaacetic acid Zinc trisodium salt use for oral drug product "for development purpose, only"

Batch number: **01010413.**
Manufacturer: **PARMAK a.s.**
Manufacture date: **04/2013** Re-test date: **04/2015**

Parameter of quality	Method code	Acceptance limit(s)	Result(s)

hameln rds a.s., Horna 26, 900 01 Modra, Slovak Republic

#8

-------- SAMPLE -----12-
05.01.01 GSL FA:1%
ID 2%DTPA
No. 3125451R

METTLER TOLEDO Balance
XP205DR Excellence Plus
SNR: 8315220381

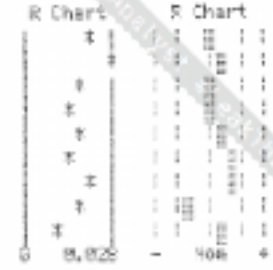
Nominal 1.040 g

1	1.051	
2	1.046	
3	1.047	
4	1.047	
5	1.051	
6	1.045	
7	1.045	
8	1.048	
9	1.047	
10	1.052	
11	1.040	
12	1.057	
13	1.055	
14	1.049	
15	1.046	
16	1.051	
17	1.050	
18	1.051	
19	1.045	
20	1.047	

X	100.85%	1.0400 g
s	0.32%	0.0033 g
Min	100.47%	1.040 g
Max	101.67%	1.057 g
R	1.15%	0.012 g
<T2-	0	0.00 %
<T1-	0	0.00 %
Marg	0	0.00 %
>T1+	0	0.00 %
>T2+	0	0.00 %
05.01.01		08:15

Stat.1: Sample# 5
X 100.52% 1.0454 g
s 0.31% 0.0095 g

R Chart X Chart



#7

-------- SAMPLE -----12-
04.01.01 GSL 23:28
ID 2%DTPA
No. 3125451R

METTLER TOLEDO Balance
XP205DR Excellence Plus
SNR: 8315220381

Nominal 1.040 g

1	1.053	
2	1.056	
3	1.055	
4	1.052	
5	1.059	
6	1.045	
7	1.043	
8	1.058	
9	1.058	
10	1.051	
11	1.055	
12	1.056	
13	1.078	
14	1.060	
15	1.048	
16	1.045	
17	1.054	
18	1.063	
19	1.061	
20	1.055	

X	101.38%	1.0355 g
s	0.96%	0.0259 g
Min	100.43%	1.045 g
Max	102.38%	1.065 g
R	1.91%	0.023 g
<T2-	0	0.00 %
<T1-	0	0.00 %
Marg	0	0.00 %
>T1+	3	15.00 %
>T2+	0	0.00 %
04.01.01		23:28

Stat.1: Sample# 7
X 100.74% 1.0477 g
s 0.68% 0.0071 g

R Chart X Chart

#6

-------- SAMPLE -----12-
08.01.01 GSL 22:16
ID 2%DTPA
No. 3124451R

METTLER TOLEDO Balance
XP205DR Excellence Plus
SNR: 8315220381

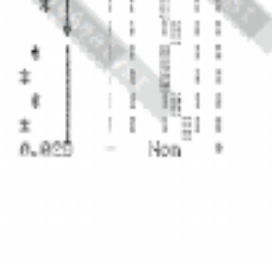
Nominal 1.040 g

1	1.050	
2	1.038	
3	1.033	
4	1.049	
5	1.039	
6	1.054	
7	1.037	
8	1.035	
9	1.059	
10	1.056	
11	1.050	
12	1.046	
13	1.054	
14	1.050	
15	1.049	
16	1.039	
17	1.051	
18	1.054	
19	1.061	
20	1.048	

X	101.58%	1.0535 g
s	2.48%	0.0042 g
Min	100.96%	1.045 g
Max	101.99%	1.061 g
R	1.41%	0.015 g
<T2-	0	0.00 %
<T1-	0	0.00 %
Marg	0	0.00 %
>T1+	0	0.00 %
>T2+	0	0.00 %
04.01.01		22:19

Stat.1: Sample# 6
X 100.04% 1.0402 g
s 0.05% 0.0006 g

R Chart X Chart



Product Name: PLACEBO FOR ZN DTPA TABLETS 400 MG
Product GMID: Batch Size: 60.0 TS (60,000 Tablets) Serial No.

IN-PROCESS TABLET WEIGHT CONTROL CHART* (10 tablets every 30 minutes using Method IM410)

*Tablet weight limits to be entered by Formulation Scientist or Supervisor/Group Leader.

Date	Time	CTNR	Operator	A+ 10% (Upper Limit) ___ g	A+ 5% (Warn Limit) ___ g	A- 5% (Warn Limit) ___ g	A- 10% (Lower Limit) ___ g

X = Wt. of 10 Tablets (Side A) O = Wt. of 10 Tablets (Side B) • (Dot) = Machine Down A = Adjustment

(1) CONTAINER NUMBER REVISED. ESK 1/19/15

Process Order No.		Batch No.	

R&PR APPROVAL
Signature & Date
Formulation Scientist
05 JAN 2015

PDS Formulations
05 Jan 2015

PDS Production

Technical Services
05 Jan 2015

QMicro

Patheon QA
05 Jan 2015

SRI International
20 JAN 2015
Signature on file

QS
20 JAN 2015

QO BATCH APPROVAL
Q.O. OK
FEB 12 2015
PER

Date of Manufacture
Recontrol Date
Expiration Date

Calculated By/Date:
Checked By/Date:

BATCH PRODUCTION RECORD
PATHEON PHARMACEUTICALS INC.

Item Code:		Serial No.

Q.O. OK
APR 27 2015
PER

Responsible Individual / Date

QA Review / Date

This document has been QA reviewed through page

Initials/Date:

Patheon

SITE: CINCINNATI DEVELOPMENT CENTER

Method Validation Protocol

Title: Diethylenetriaminepentaacetic Acid Zinc Trisodium Salt - Assay Determination and ID of Zinc and Sodium by ICP-OES

Date: 01 Oct 2013

Control No: [redacted]

Client: SRI International

Version No.: 1

Internal Approval

Prepared by:	[redacted]	
Position:	[redacted]	**Date:** 03 Oct 13
Signature:	[redacted]	
Reviewed by:	[redacted]	
Position:	[redacted]	**Date:** 03 OCT 13
Signature:	[redacted]	

Stability Report

14-MAR-2015 03:46 PM

Packaged Batch No. [redacted] **Mfg. Batch No.** [redacted] **Material Type** PLACEBO FOR ZN DTPA TABLETS 400 VG

BATCH TYPE		CONTAINER	
CLOSURE		PACKAGE DESICCANT	
MFG. BATCH #		MFG. SITE	
PKG. SITE		PKG. SIZE	
PROTOCOL #		STABILITY START DATE	18-FEB-2015

Station:	INITIAL	1 MONTH	3 MONTHS
Date Off Station:	18-FEB-2015	18-MAR-2015	18-MAY-2015
Date Testing Complete:	24-FEB-15	27-MAR-15	01-JUN-15

Operation	Limits	Units	Method	Result	Method	Result	Method	Result
DISINTEGRATION IN 0.1N HCL	NLT 16/18 NT 30	MINUTES						
ESCHERICHIA COLI	ABSENT	ABSENT/1 GRAM						
MOISTURE	REPORT	% W/W						
MOISTURE AVG	REPORT	% W/W						
MOISTURE RSD	REPORT	% W/W						
PACKAGE APPEARANCE	CONFORMS	APPEARANCE						
TABLET APPEARANCE	CONFORMS	APPEARANCE						
TOTAL AEROBIC MICROBIAL COUNT	NMT 1000	CFU/G						
TOTAL COMBINED MOLDS AND YEAST	NMT 100	CFU/G						

Method Issuance Report

Title: DTPA API / Assay and Identification by HPLC and Related Substances

Date: 14 Oct 2014

Control No.:

Client: SRI International

Version No.: 1

Internal Approval

Prepared by:		
Position:		**Date:** 16Oct14
Signature:		
Approved by:		
Position:		**Date:** 17Oct2014
Signature:		
Approval by:		
Position:		**Date:**
Signature:		

Client Approval

Name:		
Position:		**Date:**
Signature:		
Name:		
Position:		**Date:**
Signature:		

PIND
114, 317

BACKGROUND PACKAGE

Type B Pre-IND Meeting:
March 29, 2012

Product:
Pentetate Zinc Trisodium Tablets
(Zn-DTPA Tablets)
[Sodium salt of zinc diethylenetriaminepentaacetate]

Sponsor:
SRI International

Funding Agency:
National Institute of Allergy and Infectious Diseases (NIAID/NIH)

Food and Drug Administration (FDA):
Division of Medical Imaging Products (DMIP)
Office of Counter-Terrorism and Emergency Coordination (OCTEC)
Office of Orphan Drug Products (OODP)

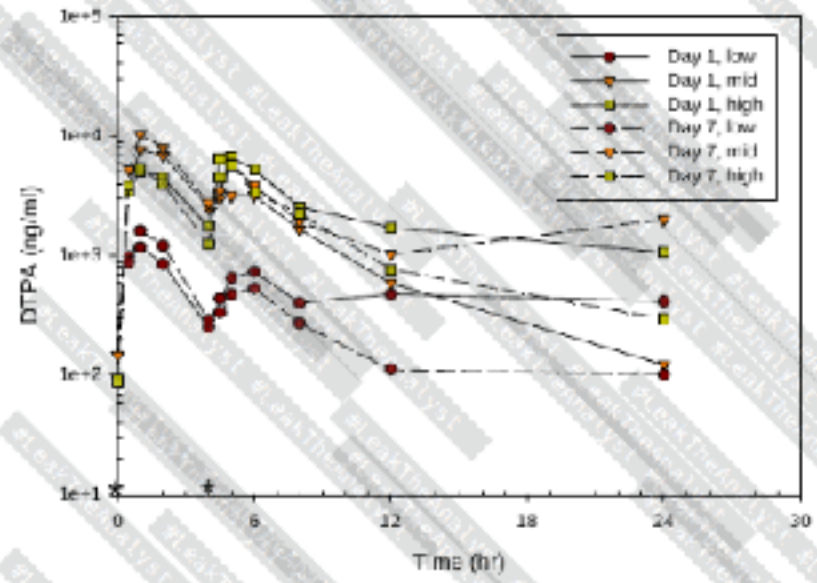


Figure 7-9. Mean plasma levels of DTPA in male Beagle dogs

	PARMAK, a.s. Na Vlčinci 16/3 OLOMOUC	Copy No: 3 Number of pages : 9 Number of enclosures -

WORKING INSTRUCTION NO. RD 183/A-4

Development project No.	ZnNa$_3$DTPA
2013-112	*Verification of the manufacturing procedure of ZnNa$_3$DTPA in the KILO-LAB.*

Elaborated by:

Date: *21.11.2012* ing. Petr Šlézar
Head of KILO-LAB

Approved by:

ing. Petr Šlézar *Head of KILO-LAB*	*RNDr. Radek Jelínek* *technologist*	*Prof. Ing. Pavel Hrabák, CSc.* *Head of R&D*

Approved: *21.11.2012*

BATCH RECORD

Batch number :	Start of production date :	End of production date :
.....	.....*27.11.2012*.....	.....*03.12.2012*.....

Analytical prescription number:	analytical protocol number :	Evaluation :
XXX	.....	...*COMPLIES*.....

Recalculated yield expected: ... ...kg

Yield obtained : ... ... kg

Notes:

Checked by :

Date : ...*05. 12. 2012*

Signature : .....

Production: *Zn-DETA*

Elaborated by: Ing. Jan Novotný

Approved by: Jiří Slavíček

UNIVERSAL BATCH RECORD

Batch number:	Start of production - date:	End of production - date:
[redacted]	29.4.2013.	14.5.2013.

Analytical prescription number:	Analytical protocol number:	Evaluation:
[redacted]	00341/13C	Complies

Yield: [redacted] kg

Details of the procedure including charges of used raw materials:

[redacted]

Notes and deviations:

[redacted]

Approved by:

Date: 09.05.13 Signature: [redacted]

Controlled by QA:

Date: 09.05.13 Signature: [redacted]

research
development
supply chain
hameln rds

CERTIFICATE OF ANALYSIS

Name of API: **$ZnNa_3DTPA$**

Diethylenetriaminepentaacetic acid Zinc trisodium salt use for oral drug product "for development purpose, only"

Batch number:
Manufacturer:
Manufacture date **04/2013** Re-test date: **04/2015**

Parameter of quality	Method	Acceptance limit(s)	Result(s)
Assay $ZnNa_3DTPA$ (HPLC)			
Assay Zinc (FAAS)			
Assay Na (FAAS)			
Microbiological quality **Total aerobic microbial count** **Total combined yeasts/moulds count** **Absence of Escherichia coli (1g)**			

Final statement:

Modra, 22nd April 2014

PharmDr. Olga Končalová
Quality Assurance Director, Qualified Person

hameln rds a.s., Horna 36, 900 01 Modra, Slovak Republic
Companies Register of the District Court Bratislava I, Section: Sa, Insert No.: [illegible]
Company ID: [illegible], Tax ID: [illegible]
Bank Account: IBAN: [illegible], BIC: [illegible]
Internet: [illegible], Tel. [illegible], Fax [illegible]

TECHNICAL PACKAGE

Diethylenetriaminepentaacetic acid Zinc trisodium salt

Issued by:	Approved by:	Approved by:	
Date: 27.05.2014	Date: 28.05.2014	Date: 27.05.2014	Date: 30.05.14

Oral and Intravenous Bioavailability of DTPA in Male and Female Beagle Dogs

Sponsor: National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
5610 Rockledge Drive, Room 4014
Bethesda, MD 20892-6601

Sponsor's Representative:

Principal Investigator:
Co-Investigator:

Testing Facility:

Study Director:

SRI Study Number:

Proposed In-Life Phase: **Start** – February 3, 2010
Finish – February 12, 2010

APPROVALS:

SRI Study Director — Date: Jan. 29, 2010

Representative Investigator — Date: 1-25-10

Bioavailability Study After Single Dose Administration of Radiolabeled DTPA (^{14}C) in Male and Female Beagle Dogs

Sponsor: National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive, Room 4014
Bethesda MD 20692-6601

Sponsor's Representative:

Principal Investigator:
Co-Investigator:

Testing Facility:

Study Director:

SRI Study Number:

Proposed In-Life Phase: Start – March 5, 2008
Finish – March 7, 2008

APPROVALS:

March 4, 2008
Date

03/03/08
Date

Bioavailability of Oral and Intravenous Formulations of ^{14}C-DTPA as Compared with Commercial Products in Male Sprague-Dawley Rats

Sponsor: National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive, Room 4014
Bethesda, MD 20892-6601

Sponsor's Representative:

Principal Investigator:
Co-Investigator:

Testing Facility:

Study Director:

SRI Study Number:

Proposed In-Life Phase:

APPROVALS:

01/24/08
Date

01/24/08
Date

Excretion of Iron after Repeat Dose Administration of DTPA in Male and Female Beagle Dogs

Sponsor:

National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive, Room 4014
Bethesda MD 20892-6601

Testing Facility:

SRI International

Final Report • October 14, 2014

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATION OF PLASMA CONCENTRATIONS OF DTPA IN FY11-038D

Authors:

Testing Facility:
SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

SRI Study Number:

SRI Project Number:

Sponsor:
National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive, Room 4014
Bethesda, MD 20892-6601

Sponsor's Representative:

NIAID Contract Number: HHSN272201000029C

Radionuclide Efficacy Protocol

This study will NOT be performed according to Good Laboratory Practices (GLP) Regulations as described in the United States Code of Federal Regulations (CFR) – 21 CFR Part 58. The Lovelace Respiratory Research Institute's (LRRI) animal research facilities are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. However, LRRI standard operating procedures (SOPs) will be followed.

Table Of Contents

Protocol Number	FY11-038C
Title	Evaluating the Efficacy of Therapeutic Regimen with Ca-DTPA and Zn-DTPA for Removing Systemically Distributed Plutonium from the Body After Face Mask Inhalation in Male and Female Beagle Dogs
Test Facility	Lovelace Respiratory Research Institute (LRRI) 2425 Ridgecrest Dr SE Albuquerque, NM 87108 Courier Address and Location of Laboratory: Bldg 9217, Area Y Kirtland Air Force Base Albuquerque, NM 87115
Key Personnel	

Appendix A

EVALUATING THE EFFICACY OF THERAPEUTIC REGIMEN WITH ZNDTPA MINI-TABLETS FOR REMOVING AMERICIUM FROM THE BODY AFTER NOSE-ONLY INHALATION IN MALE AND FEMALE F344 RATS

Evaluating the Efficacy of Therapeutic Regimen with ZnDTPA Mini-tablets for Removing Americium From the Body after Nose-Only Inhalation in Male and Female F344 Rats

Final Report
LRRI Study Number:

To

Lovelace Biomedical and Environmental Research Institute (LBERI)
2425 Ridgecrest Drive SE
Albuquerque, NM 87108

Courier Address and Location of Laboratory:
Bldg 9217, Area Y
Kirtland Air Force Base
Albuquerque, NM 87115

Study Initiation Date: 23 May 2011

Final Report Date of Issue: 16 March 2012

SIGNATURES

Evaluating the Efficacy of Therapeutic Regimen with ZnDTPA Mini-tablets for Removing Americium From the Body after Nose-Only Inhalation in Male and Female F344 Rats

Final Report
LRRI Study Number:

To

Lovelace Biomedical and Environmental Research Institute (LBERI)
2425 Ridgecrest Drive SE
Albuquerque, NM 87108

Courier Address and Location of Laboratory:
Bldg 9217, Area Y
Kirtland Air Force Base
Albuquerque, NM 87115

Study Initiation Date: 23 May 2011

Final Report Date of Issue: 16 March 2012

SIGNATURES

Evaluating the Efficacy of Therapeutic Regimen with Ca-DTPA and Zn-DTPA for Removing Systematically Distributed Plutonium from the Body After Facemask Inhalation in Male and Female Beagle Dogs

Final Report
LRRI Study Number: [redacted]

To

[redacted]

SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025-3493

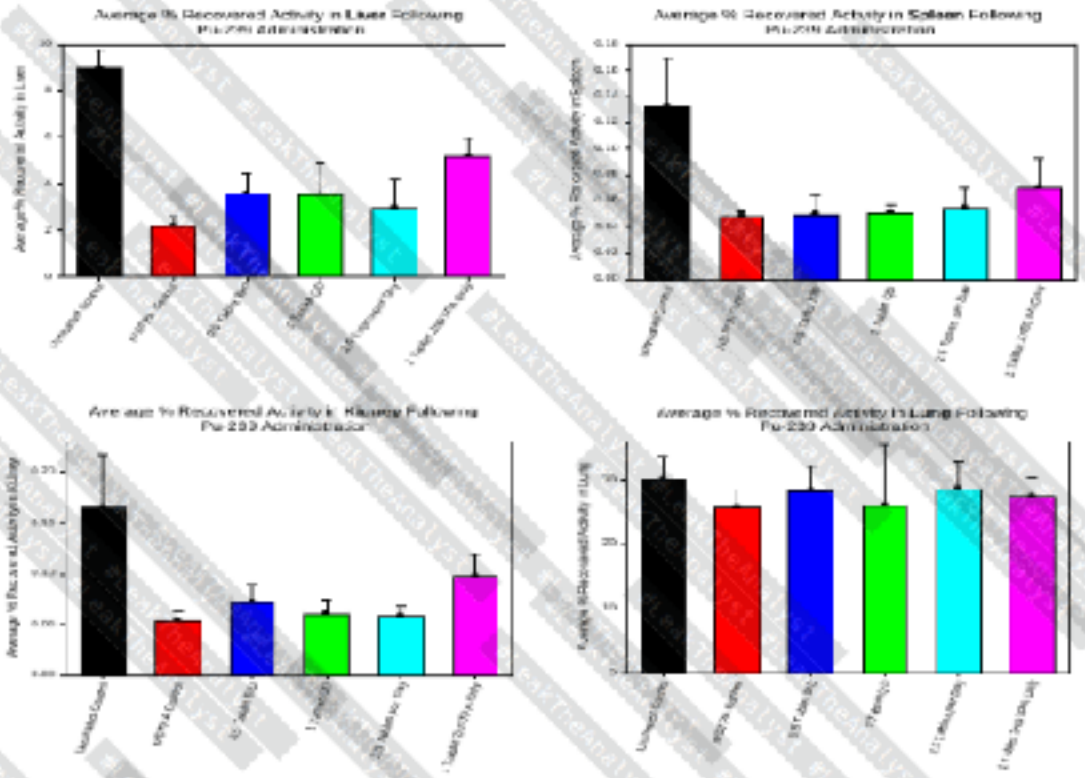


Figure 4.

Table 5a. Average Percent Recovered Activity

Group	Liver	Spleen	Kidney	Lung
Untreated Control				
IV Zn-DTPA				
½ tablet, BID				
1 tablet, QD				
2.5 tablets (1.5 in AM and 1 in PM)				
1 tablet, QD (no IV Ca-DTPA)				

DTPA

Final Report • January 14, 2013

7-DAY ORAL TABLET MAXIMUM TOLERATED DOSE TOXICITY AND TOXICOKINETIC STUDY OF ZN-DTPA IN MALE AND FEMALE BEAGLE DOGS

Authors:

Testing Facility:
SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

SRI Study Number:
SRI Project Number:

Study Initiation: August 24, 2012

Experimental Work Performed:
Start: September 11, 2012
Finish: November 26, 2012

Study Completion: January 14, 2013

Sponsor:
National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive Room 4014
Bethesda, MD 20892-6601

Sponsor's Representative:

NIAID Contract Number:

Table F-3 (Concluded)
Plasma Drug Levels

Males
7560 mg/dog PD

Dog No.	Day	Time (hr)	[DTPA] (ng/ml)	Mean [DTPA] (ng/ml)
13	7	0		
14	7	0		
13	7	1		
14	7	1		
13	7	3		
14	7	3		
13	7	6		
14	7	6		

Females
7560 mg/dog PD

Dog No.	Day	Time (hr)	[DTPA] (ng/ml)	Mean [DTPA] (ng/ml)
15	7	0		
16	7	0		
15	7	1		
16	7	1		
15	7	3		
16	7	3		
15	7	6		
16	7	6		

Final Report • April 30, 2008

7-DAY REPEAT DOSE TOXICITY STUDY OF DTPA TO SPRAGUE-DAWLEY RATS

Author:

Testing Facility
SRI International
Biosciences Division
333 Ravenswood Avenue
Menlo Park, CA 94025

SRI Study Number:
SRI Project Number:

Study Initiation: November 30, 2007

Experimental Work Performed:
Start: December 7, 2007
Finish: January 21, 2008

Study Completion: TBD

Sponsor:
National Institute of Allergy and Infectious Diseases
Division of Allergy, Immunology, and Transplantation
6610 Rockledge Drive, Room 4014
Bethesda, MD 20892-6603

Sponsor's Representative:

NIAID Contract No. | **ADB Contract No.**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

March 27, 2012

CONFIDENTIAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF MEDICAL IMAGING PRODUCTS

PRELIMINARY COMMENTS TO THE SPONSOR

SRI International
Attention:
Associate Director, Regulatory Affairs
333 Ravenswood Avenue
Menlo Park, California 94025
Zn-DTPA Tablets

Please refer to your meeting request dated January 6, 2012, received January 6, 2012, requesting a meeting, with the Division of Medical Imaging Products (DMIP) to discuss the development and registration program for Zn-DTPA tablets.

As noted in the Division's January 23, 2012, "Meeting Granted" letter, based on the submitted statement of purpose, objectives, and proposed agenda, we considered the meeting a type B face-to-face meeting as described in our guidance for industry titled "Formal Meetings with Sponsors and Applicants for PDUFA Products.

Reference is also made to the meeting background package dated February 28, 2012. This submission will serve as the basis for discussions during the March 29, 2012 12:00 Noon to 1:30 PM, scheduled face-to-face meeting. We have completed the review of this submission and have the following preliminary comments.

These comments should not be considered as an official FDA position. They are meant to promote and facilitate a collaborative and successful exchange during the upcoming face-to-face meeting.

If these comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting by contacting the Regulatory Project Manager and providing your responses to our comments in writing.

Product Name: ZN DTPA TABLETS 400 MG
Product GMID: [redacted] Batch Size: [redacted] 2016 tablets

COMPRESSION PROCESS MONITORING TABLE

	Main Pressure (kN)	Pre-Pressure (kN)	Press Speed RPM	Paddle Speed RPM	Fill Depth (mm)	Stage 1 (mm)	Stage 2 (mm)	Performed By/Date
1) Start								
2) ~~15 min~~								
3) ~~30 Min~~								
4) 45 Min								

Formulation Trial Record

Client: SRI International

Project: SRI International Zn DTPA Tablets

Product: Zn DTPA Tablets active

Lot Number: I

Internal Approval (Post Production)		
Prepared by:		**Date:** 9/17/14
Signature:		
Reviewed by:		**Date:**
Signature:		

Number of Attachment Pages: ___

Date Manufacturing Started: 9/10/14

Date Manufacturing Completed: 9/12/14

Date Scanned: _____

(1)

TPJ 9/11/14

Patheon

SITE: CINCINNATI DEVELOPMENT CENTER

Method Validation Report

Title: Diethylenetriaminepentaacetic Acid Zinc Trisodium Salt / Identification and Assay of Zinc and Sodium by ICP-OES

Date: 23 OCT 2013

Control No:

Client: SHI International

Version No.: 1

Internal Approval

Prepared by:		
Position:		Date: 31 Oct 13
Signature:		
Reviewed by:		
Position:		Date: 31 OCT 13
Signature:		
Approved by:		
Position:		Date: 31 Oct 2013
Signature:		

Client Approval

Approved by:		
Position:	Director of Quality Assurance	Date:
Signature:	See Attached	
Approved by:		
Position:	PI & Director of Formulation	Date:
Signature:	See Attached	

Analytical Report 1: Typical ICP-OES Report

Page 1 of 3

ICP-OES Rev 11 Report

Worksheet creation date Tuesday, October 22, 2013
All Data Report 10/22/2013 9:38:06 AM
Varian Vista PRO ICP-OES
Instrument serial number -
Computer name -

Date Time: 10/22/2013, 9:25:05 AM
Printed By: All Users Group\AD Users Projects\user12713 (Operator)
Authorised By:
Description: print

Method Parameters

Wavelength Calibration
Worksheet D:\ICP\ICPVarian\VAIMDE Supplied Worksheets\000\Supplied Worksheet.Vws
Last Correction Time:
Alignment Offset:
Maximum Error:
Percent Calibration Lines Used:
Drift:
Last Measurement:

Analysis Lines

Label		Wavelength	Type	IS	Bkg Mode	PPF	OSCL	ORCP
Na 588.995								
Na 589.592								
Zn 213.857								

Conditions Sets (All lines share a single condition set)

Power (kW)	Plasma flow (L/min)	Aux flow (L/min)	Neb flow (L/min)	Replicate Time (s)	Stab Time (s)	View Height (mm)

Sample Introduction

Sample Uptake (s)	Rinse Time (s)	Pump Rate (rpm)	Fast Pump

General Settings
Replicates
3

Blank (BR) 10/8/2013, 10:56:49 AM Rack 1, Tube 1

Label	Soln Conc.	Units	SD (or %RSD)	Int. (c/s)
Na 589.592				
Na 588.995				
Zn 213.857				

Performance the World Over

Patheon

Patheon Pharmaceuticals Inc.
2110 East Galbraith Road
Cincinnati, Ohio 45237-1625 USA

Patheon.com

CERTIFICATE OF ANALYSIS

PRODUCT: Placebo for ZN DTPA Tablets 400 mg
MFG. BATCH NO.:
ITEM CODE NO.:
MFG. DATE: 13-Jan-2015
MANUFACTURED FOR: SRI International, Menlo Park, CA

TESTS:	METHOD:	SPECIFICATIONS:	RESULTS:

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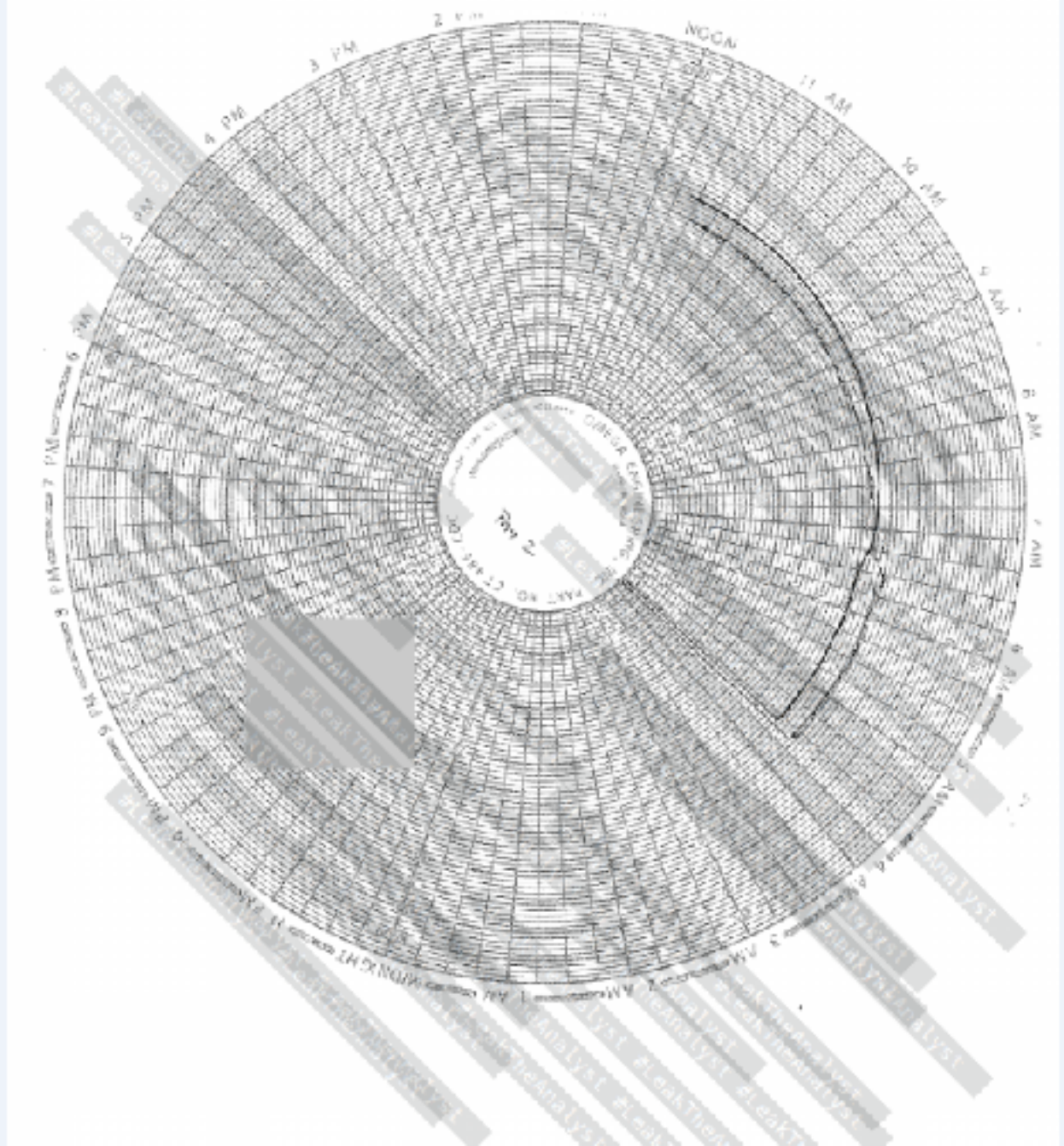

Patheon.

SRI CINCINNATI DEVELOPMENT CENTER

Method Transfer Protocol

Title: GTPA API and Tablets / Assay, Blend Uniformity, Content Uniformity and Identity by HPLC

Date: 01 Oct 2013

Control No.:

Client: SRI International

Version No.: 1

Internal Approval

Prepared by:	Courtni J. Webb	
Position:		Date: 01 Oct 2013
Signature:		
Approved by:		
Position:		Date: 10/1/2013
Signature:		
Approved by:		
Position:		Date: 01 Oct 2013
Signature:		

Client Approval

Name:		
Position:	Director of Quality Assurance	Date:
Signature:	See Attached	
Name:		
Position:	PI & Director of Formulation	Date:
Signature:	See Attached	

Stability Report

23-APR-2015 10:12 AM

Packaged Batch No. [redacted] **Mfg. Batch No.** [redacted] **Material Type** ZN DTPA TABLETS 400 MG

BATCH TYPE	CLINICAL BATCH	CLOSURE	
CONTAINER	[redacted] - WHITE 120ML HDPE BOTTLE	PACKAGE DESICCANT	
MFG. BATCH #	[redacted]	MFG. SITE	
PKG. SITE	CINCINNATI	PKG. SIZE	50 COUNT
PROTOCOL #	[redacted]	STABILITY START DATE	18-FEB-2015

Station:			INITIAL		1 MONTH	
Date Off Station:			18-FEB-2015		25-MAR-2015	
Date Testing Complete:			24-MAR-15		21-APR-15	
Operation	**Limits**	**Units**	**Method**	**Result**	**Method**	**Result**