

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204781Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 204-781**

**DOTAREM® (Gadoterate meglumine) Injection**  
**376.9 mg/mL**

**Guerbet, LLC**  
**Bloomington, IN 47403**

**Milagros Salazar, Ph.D.**

**Office of New Drug Quality Assessment**  
**Division III Premarketing, Branch VII**

**For**  
**Division of Medical Imaging Products**

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# Chemistry Review Data Sheet

1. NDA #: 204-781
2. REVIEW #: 1
3. REVIEW DATE: 20-FEB-2013
4. REVIEWER: Milagros Salazar, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original, SD-1	20-SEP-2012
SD-3	31-Oct-2012
SD-4	31-Oct-2012
SD-5	06-Nov-2012
SD-8	31-Dec-2012
SD-11	01-Feb-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Guerbet, LLC

Address: 1185 West 2<sup>nd</sup> Street  
Bloomington, IN 47403

Representative: Corina Harper, RAC  
Head of North America Medical and Regulatory Affairs

Telephone: 812-333-0059 x211 (b) (4)

FAX/Email: 812-333-0084 / corina.harper@guerbet-group.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: DOTAREM®
- b) Non-Proprietary Name (USAN): Gadoterate meglumine (USAN ZZ-155)
- c) Code Name/#: P449
- d) Chem. Type/Submission Priority: (1) NME / (P) Priority

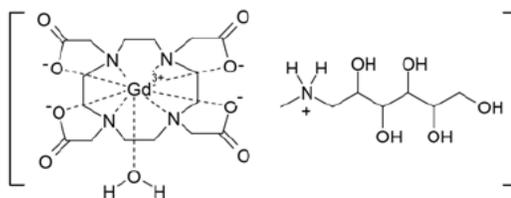
## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: MRI contrast media
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 376.9 mg/mL
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemical Name:

D-glucitol,1-deoxy-1-(methylamino)-,[1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)-kappa.N1, kappa.N4, kappa.N7, kappa.N10, kappa.O1, kappa.O4, kappa.O7, kappa.O10]gadolinium(1-) (1:1)

## Structural Formula:



Molecular Formula: C<sub>23</sub>H<sub>42</sub>O<sub>13</sub>N<sub>5</sub>Gd  
Relative Molecular Mass: 753.86 g/mol

CAS number: 92943-93-6

## Other Names:

Gadoterate meglumine  
DOTA-Gd meglumine  
Meglumine salt of gadoteric acid  
Meglumine salt of the 1, 4, 7, 10 tetraazacyclododecane N, N', N'', N'''-tetraacetic acid gadolinium complex

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sub>1</sub>	STATUS <sub>2</sub>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	3/31/2008	LoA 1-Jul-2008
	II		1	Adequate	12/14/2012	LoA 20-Jan-2012	
	III		1, 4	Adequate	1/28/2011	LoA 22-Sep-2011	
	III		3	Adequate	1/19/2011	LoA 17-Oct-2-11	
	III		3	Adequate	6/8/2012	LoA 19-Sep-2011	
	V						
	III		3	Adequate	8/30/2012	LoA 2-Sep-2011	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no major revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> 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
Exclusivity request under 21 CFR § 314.108(b)(2)	NDA 204-781 original Section 1.3.5.3.	Guerbet claims five years exclusivity for DOTAREM under 21 CFR § 314.108(b)(2) as required by 21 CFR § 314.50(j)(3)
Patent Certification	NDA 204-781 original Section 1.3.5.2.	No certification given. The drug and investigations described in 21 U.S.C. § 355(b)(1)(A) which are the basis for approval were conducted by or for the applicant and this application is not an abbreviated application for a new drug.

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Satish Misra, Ph.D.
EES- Office of Compliance	Pending		Derek Smith, Ph.D.
Pharm/Tox	Pending		Olayinka Dina, Ph.D.
Biopharm	N/A		
LNC	N/A		
Methods Validation	Provided- FDA validation not requested.		Milagros Salazar, PhD.
DMEPA*	Acceptable name		Kevin Wright, Pharm.D.
OPDP** Proprietary name	Approval	12-Jan-2012	
OMEPRM/DRISK***	Pending		
Division of Pharmacovigilance II	Acceptable		Michael E. Kieffer, Pharm. D., M.A.
EA- categorical exclusion requested under 21 CFR 25.31(a)	Categorical exclusion granted. The basis for the request are acceptable. (section 1.12.14, orig. NDA)	20-Feb-2013	Milagros Salazar, PhD.
Microbiology	Approval	11-Feb-2013	Vinayak Pawar, Ph.D.
OC-OMPQ Div. GMP assessment	Pending	24-Jan-2013	Derek Smith, Ph.D. x 6-5321
CDRH thru –Office of Combination Products	Pending		

\* DMEPA: Division of Medication Error Prevention and Analysis

\*\* Office of Prescription Drug Promotion (formerly DDMAC)

\*\*\*Office of Medication Error, Prevention and Risk Management / Div. of Risk Management

## Chemistry Review Data Sheet

## Establishment Inspection Request – Sites Identified in the NDA

Registration No. DUNES No.	Name and Address	Manufacturing Function	Status
			(b) (4) Ready for Inspection
			Ready for Inspection
			Ready for Inspection
			Ready for Inspection

**19. ORDER OF REVIEW** (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes  
\_\_\_ No If no, explain reason(s) below:

# The Chemistry Review for NDA 204-781

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Based on the chemistry, manufacturing and controls, including microbiological quality, this application for a new molecular entity is recommended for approval pending satisfactory recommendations from the office of compliance and office of combination products/ CDRH consult under 505(b)(1). The products expiration time was requested for (b) (4) but the stability data did not support this expiry for all DOTAREM products. Therefore, there is a recommendation for approval of specific shelf life for different products. (see section C. Basis for Approvability).

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

None

### II. Summary of Chemistry Assessments

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

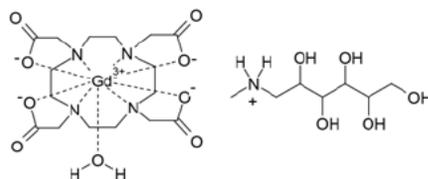
##### Drug Substance

Gadoterate meglumine is the active pharmaceutical ingredient responsible for the diagnostic activity of DOTAREM as a magnetic resonance imaging (MRI) contrast agent; it is formed (b) (4)

(b) (4)

Gadoterate

meglumine is chemically designated as D-glucitol, 1-deoxy-1-(methylamino)-, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)- kappa.N1, kappa.N4, kappa.N7, kappa.N10, .kappa.O1, kappa.O4, .kappa.O7, kappa.O10]gadolate(1-) (1:1); it has a molecular formula  $C_{23}H_{42}O_{13}N_5Gd$  and a relative molecular mass of 753.86 g/mol. Structural formula in solution:



(b) (4)

## Chemistry Assessment Section

(b) (4)

Gadoterate is the first in the GBCA class to be a macrocyclic ionic complex of gadolinium (-1). The thermodynamic stability constant,  $\text{Log } K_{\text{therm}}$  of gadoterate is 25.6 while its conditional stability constant at pH 7.4,  $\text{Log } K_{\text{cond}}$  is 19.3; its kinetic stability (dissociation half-life at pH 1.0 at 25°C) is 338 hours. These physicochemical characteristics are important for the high in-vitro stability of gadoterate which has been associated with its in-vivo stability towards transchelation and toxicity in animal models and humans when compared to other GBCA agents. Relaxation constants (b) (4)

(b) (4)

DOTA the final intermediate is manufactured by (b) (4) and (b) (4) these sites were inspected by FDA.

Gadoterate meglumine is synthesized (b) (4) these sites were inspected by FDA.

**Drug Products - Vials and syringes**

DOTAREM Injection is formulated as a ready-to-use aqueous, sterile, pyrogen free solution for intravenous administration. DOTAREM 379.9 mg/mL (equivalent to 0.5 mmol/mL) has the following composition per milliliter: (b) (4)

(b) (4)

The active ingredient gadoterate meglumine is formed (b) (4)

(b) (4)

The presentations of this product include unit and multiple dosage forms in glass vials and prefilled syringes as follows:

10mL, 15mL and 20mL vials (small volume parenteral- single dose)  
NDC#s 67684-200-01, 67684-200-02 and 67684-200-03 respectively.

10mL, 15mL and 20 mL prefilled syringes, PFS, (small volume parenteral- single use)  
NDC#s 67684-300-01, 67684-300-02 and 67684-300-03 respectively.

100mL vial (large volume parenteral- multiple doses)-Pharmacy Bulk Package, PBP  
NDC# 67684-200-04.

## Chemistry Assessment Section

DOTAREM Injection is manufactured by (b) (4) and (b) (4) these sites were inspected by FDA. The product is made using (b) (4)

A (b) (4) expiration period was requested for all DOTAREM products. However, the stability data provided does not support such shelf life. The expiration periods recommended for the approval of DOTAREM products, based on the stability data presented, are selectively from 18 months to 30, to 36 months. (see section C. Basis for Approvability)

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

DOTAREM (gadoterate meglumine) Injection 0.5 mmol/mL for intravenous administration is proposed for use as a gadolinium contrast agent (GBCA) in the MRI of brain (intracranial), spine and associated tissues on adults and pediatric patients (from neonates to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity. The recommended dose for adults and children (neonates and older) is 0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approx. 2 mL/sec for adults and 1-2 mL/second for children. Contrast-enhanced MRI can begin immediately following DOTAREM injection.

For the pharmacy bulk package (PBP) preparation the following practices are required: 1) the transfer of DOTAREM from the PBP should be done in an aseptic work area, such as laminar flow hood and using aseptic technique and suitable transfer device. The closure should be penetrated only once, 2) once the container closure is punctured, the PBP should not be removed from the aseptic area, 3) each individual dose should be immediately used after withdrawal from the PBP, 4) the contents of the PBP should be used within 24 hours after initial puncture.

### C. Basis for Approvability

Based on 505(b)(1) of the Act, adequate chemistry, manufacturing and controls are presented in this application to assure the identity, purity, quality and strength of DOTAREM Injection products.

A (b) (4) expiration period was requested for all DOTAREM products. However, the stability data provided does not support such shelf life. The following expiration periods are recommended for approval of DOTAREM products based on the stability data presented:

- Vials 10 mL, 15 mL, 20 mL and 100mL ..... 30 months expiry  
manufactured at (b) (4) with DOTA from (b) (4)
- Vials 10 mL, 15 mL, 20 mL and 100mL ..... 18 month expiry  
manufactured at (b) (4) with DOTA from (b) (4)
- PFS 10 mL, 15 mL and 20 mL ..... 36 months expiry  
manufactured at (b) (4) with DOTA from (b) (4)
- PFS 10 mL, 15 mL and 20 mL ..... 18 month expiry  
manufactured at (b) (4) with DOTA from (b) (4)

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Chemist/Milagros Salazar, Ph.D./Date:  
ChemistryCMCLead/ Eldon Leutzinger, Ph.D./Date:  
ONDQA Division Director/Eric Duffy, Ph.D./Date:

### C. CC Block

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/s/  
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MILAGROS SALAZAR DRIVER

02/20/2013

CMC recommendation: Approval pending acceptable recommendations from the office of compliance and office of combination products/ CDRH consult.

ELDON E LEUTZINGER

02/20/2013

ERIC P DUFFY

03/07/2013

**NDA FILEABILITY CHECKLIST**  
**PRODUCT QUALITY**

NDA#: 204-781

Applicant: Guerbet, LLC

Stamp Date: 20-Sep-2012

Drug Name: DOTAREM® (Gadoterate Meglumine) Injection, 376.9 mg/mL  
For Intravenous Administration

Presentation/Strength: Vials of 10 mL, 15 mL, 20 mL (b) (4) and 100 mL (b) (4)  
Pre-filled syringes of 10 mL, 15 mL and 20 mL (b) (4)

PDUFA Date: 20-Jul-2013

Filing Date: 19-Nov-2012

74-Day Filing Issues: 3-Dec-2012

Chem Type / Priority: 1 (NME) / S

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical Exclusion is requested.
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		(b) (4) This is considered to be a review issue.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		The formulation proposed in this NDA has been approved in Europe since 1989 and (b) (4)
14	Is there a Methods Validation package?	√		
15	Is a separate Microbiological section included?	√		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.. N/A

Review Chemist: Milagros Salazar, Ph.D.

Date: 12-Oct-2012

CMC Lead: Eldon Leutzinger, Ph.D.

Date: 12-Oct-2012

Have all DMF References been Identified? YES

DMF Number	Holder	Description	LOA Included	Status
			1-Jul-2008	Active (2006)
			20-Jan-2012	Active (1978)
			22-Sep-2011	Active (2007)
			17-Oct-2-11	Active (1998)
			19-Sep-2011	Active (1981)
			2-Sep-2011	Active (2001)

\*



(b) (4)

Establishment Inspection Request – Sites Identified in the NDA

Registration No. DUNES No.	Name and Address	Manufacturing Function	Status
			(b) (4) Ready for Inspection
			Ready for Inspection
			Ready for Inspection
			Ready for Inspection

<sup>1</sup> Contact:

<sup>2</sup> Contact:

<sup>3</sup> Contact:

<sup>4</sup> Contact:



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/s/  
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MILAGROS SALAZAR DRIVER  
10/14/2012  
Recommendation: NDA is fileable.

ELDON E LEUTZINGER  
10/15/2012  
For Ali H Alhakim



**Formulation:**

Each milliliter of the formulation (single-dose glass vials, single-dose glass syringes and pharmacy bulk package) contains the following ingredients. See next review page.

376.93 mg of Gadoterate Meglumine, and corresponds to the following composition:

(b) (4) of DOTA (b) (4)  
(b) (4) of Gadolinium Oxide  
(b) (4) of Meglumine (b) (4)  
(b) (4) of Water for Injection USP

The glass in vials and syringes is USP Type 1. Stopper in vials is (b) (4)  
Vials are sealed with an (b) (4) The tip cap in the pharmacy bulk package is of (b) (4)  
(b) (4) and the plunger stoppers are of (b) (4)



Below, I am showing a table with the usual elements that are considered for determining the filing status of the NDA, based on the key pieces of information (as listed). Generally, for the IQA, I do look through the CMC section of the NDA for the applicable sections for which there is either enough or absence of enough information (and its sufficiency) for the start of a comprehensive review. This is based on an “initial” review, and is not a final decision.

**INITIAL ASSESSMENT - FILING:**  
(the final decision for filing will be left to the CMC Review Team)

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street addresses</u> and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Stated in a table listing all of the establishments
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		But, there is some lack of batch data – will be assessed by primary reviewer. Based on the good profile of stability (largely established in Europe), this may not rise to the level of a filing issue.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		But, there will be review issues.
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		Part of the analytical section
15	Is a separate Microbiological section included?	X		
16	Have all consults been identified and initiated?	X		

CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 10/11/2012  
Division of New Drug Quality Assessment III, Branch VII

Division Director: Eric Duffy, Ph.D.  
Division of New Drug Quality Assessment III

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/s/  
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ELDON E LEUTZINGER  
10/11/2012

ERIC P DUFFY  
10/12/2012