

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-090**

**CHEMISTRY REVIEW(S)**

## ONDQA Division Director's Memo

NDA 22-090  
EOVIST<sup>®</sup> (gadoxetate disodium injection)  
Date: June 11, 2008

### Introduction

EOVIST<sup>®</sup> (Gadoxetate disodium injection) is a ready to use solution for injection and is supplied (as approved) in glass vials (10 mL fill) — for use magnetic resonance imaging of the liver in adult patients. EOVIST is a single-use drug product.

**ONDQA recommends approval.**

### Administrative

The NDA was received 12-JUN-2007 was assigned a standard review status (1S). All CMC review activities were completed as of 29-APR-2008 (secondary sign-off).

### Drug Substance and Drug Product

The drug substance (gadoxetate disodium) is a complex between gadolinium (Gd<sup>3+</sup>) and (4s)-4-ethoxybenzyl-3-6-9-tris-(carboxylatomethyl)-3,6,9-triazaundecanoic acid. Each mL of the drug product contains 181.43 mg of gadoxetate disodium buffered to pH — to

There are no pending CMC issues

**Phase-4 Commitment: NONE**

Rik Lostritto, Ph.D., Director  
ONDQA, Division-III

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/s/

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Richard Lostritto  
6/11/2008 04:36:26 PM  
CHEMIST



**GADOXETATE DISODIUM INJECTION**

**Eldon E. Leutzinger, Ph.D.**  
**Pharmaceutical Assessment Lead**

**OFFICE OF NEW DRUG QUALITY ASSESSMENT  
DIVISION OF PREMARKETING ASSESSMENT AND  
MANUFACTURING SCIENCE (BRANCH V)**

**CMC REVIEW OF NDA 22-099**

**FOR THE DIVISION OF MEDICAL IMAGING AND HEMATOLOGY  
PRODUCTS (HFD-160)**



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# Chemistry Review Data Sheet

1. NDA 22-099
2. REVIEW # 1
3. REVIEW DATE: 04/21/2008
4. REVIEWER: Eldon E. Leutzinger, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	12-Jun-2007
Amendment N000-BC	06-Dec-2007
Facsimile	18-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer Healthcare Pharmaceuticals, Inc.  
Address: P.O. Box 1000  
Representative: 340 Changebridge Road  
Telephone: (973) 487-2073 (Sibylie Jennings, Global  
Regulatory Affairs)

8. DRUG PRODUCT NAME/CODE/TYPE:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- a) Proprietary Name: Not yet determined
- b) Non-Proprietary (Established Name): Gadoxetate Disodium
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Contrast for MRI

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 0.25 mol / L

13. ROUTE OF ADMINISTRATION: Intravenous Injection

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: (4S)-4-ethoxybenzyl)-3,6,9-tris-(carboxylatomethyl)-3,6,9-triazaundecanoic acid, Gd

CAS Registry No: 135326-22-6

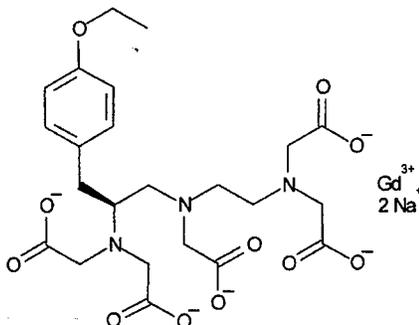
Schering AG code No: ZK139834

Molecular Formula:  $C_{23}H_{28}N_3O_{11} \cdot Gd \cdot 2Na$

Molecular Weight: 752.72

Molecular Structure: See next page

## Chemistry Review Data Sheet



Gd-EOB-DTPA

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
_____	II	Bayer*	_____	1	Adequate	01/28/2008	
_____	II	_____	_____	1	Adequate	04/02-3008	

\* Bayer Healthcare Pharmaceuticals Inc, 340 Changebridge Road, P.O. Box 1000, Montville, NJ 07045-1000

\*\*

<sup>1</sup> 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")

<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:**



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	9/24/2007	Office of Compliance
Pharm/Tox	Pending		Yanli Ouyang, Ph.D.
Biopharm	Pending		Christy John, Ph.D.
LNC	N/A		
Methods Validation	Not needed	3/20/2008	Eldon E. Leutzinger, Ph.D.
DEMETS	Tradename ("Primovist") not recommended – misleadingly implies superiority to other treatments	7/26/2007	Linda M. Wisniewski, RN
EA	Acceptable	3/20/2008	Eldon E. Leutzinger, Ph.D.
Microbiology	Approval	1/04/2008	Bryan S. Riley, Ph.D.

#### OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 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 22-090

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

CGMP inspections for facilities are completed and acceptable (9/24/2007). All CMC issues have been fully resolved. NDA 22-90 is recommended for APPROVAL for the 10 mL fill in 10 mL glass vial, as shown in the current labeling (April 18, 2008). The approval letter should

with a 60 months expiration dating period. The product can be approved

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

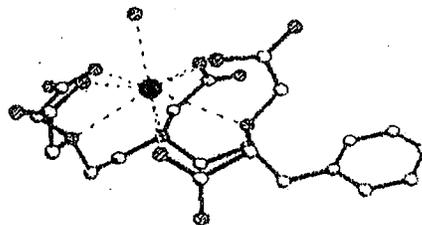
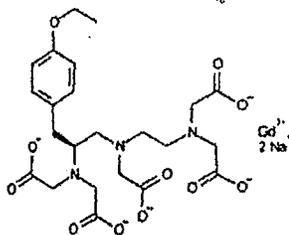
N/A

### II. Summary of Chemistry Assessments

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

Gadoxetate disodium Injection is a "ready to use" solution for injection and is supplied in both glass vials. Each mL of the formulation contains 181.430 mg of Gadoxetate disodium (active ingredient), Caloxetate trisodium, (tromethamol) in WFI, and adjusted to pH with hydrochloric acid and sodium hydroxide. The concentration of Gadoxetate disodium is 0.25 mol/L.

Gadoxetate is a complex between gadolinium ( $Gd^{3+}$ ) and (4S)-4-ethoxybenzyl)-3,6,9-tris-(carboxylatomethyl)-3,6,9-triazaundecanoic acid (EOB-DTPA).



## Executive Summary Section

10<sup>22</sup>, respectively), an order of approximately 10.

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

Bayer intends to launch marketing with the Gadoxetate disodium Injection filled in 10 mL glass vials (with 10 mL fill). The composition per mL is indicated in Part A. This product is indicated for use in magnetic resonance imaging (MRI) of the liver in adult patients the T1-weighted images. detection, characterization of focal liver pathologies metaseses. The product is intended as single use.

**C. Basis for Approvability or Not-Approval Recommendation**

(Basis for Approval).

A method will be used to manufacture Gadoxetate disodium Injection. This method involves:

The product has been shown to remain stable in the given formulation under normal conditions of storage for at least 60 months. Based on these studies, their proposed expiration dating period is 60 months.

There were some labeling issues for CMC that have been resolved; these included



Executive Summary Section

\_\_\_\_\_

**III. Administrative**

A. Reviewer's Signature

Eldon E. Leutzinger, Ph.D.

B. Endorsement Block

CMC Reviewer's Name / Eldon E. Leutzinger, PhD.

CMC Branch Chief Name / Ravi S. Harapanhalli, Ph.D.

C. CC Block

DMIHDP Project Manager Name / James Moore, PharmD., M.A.

ONDQA Project Manager Name / S.Golde.

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   Draft Labeling

   Deliberative Process

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/s/

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Eldon Leutzinger  
4/22/2008 12:54:30 PM  
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Ravi Harapanhalli  
4/29/2008 02:35:30 PM  
CHEMIST

Initial Quality Assessment (IQA)  
Branch V

Pre-Marketing Assessment and Manufacturing Science Division III  
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging and Hematology Drug Products  
NDA: 22-090  
Applicant: Bayer Healthcare Pharmaceuticals, Inc.  
Stamp Date: 07/12/2007  
PDUFA Date: 05/02/2008  
Trademark: Primovist  
Established Name: Gadoxetate Disodium  
Dosage Form: Sterile solution  
Route of Administration: Injection  
Indication: "Magnetic resonance imaging (MRI) of the liver in adult patients — the T1-weighted images — detection — and characterization of focal liver pathologies — in a pre-surgical evaluation."

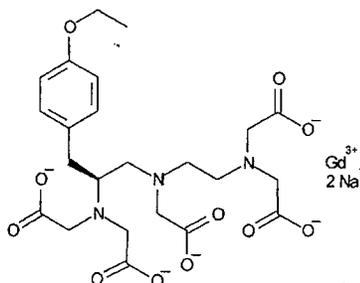
Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D.

	YES	NO
ONDQA Fileability:	X	
Comments for 74-Day Letter		X

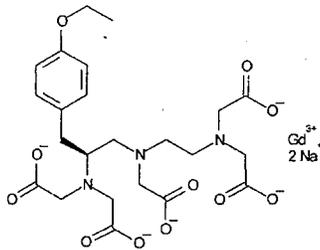
Summary and Critical Issues:

A. Summary

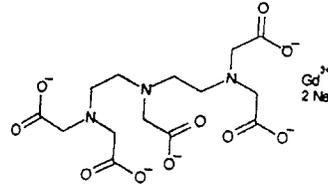
Primovist Injection is an aqueous solution of "Gadoxetate Disodium," or gadolinium EOB-DTPA as disodium salt (Drug Substance). A depiction of the molecular structure is shown as follows, as reproduced from the NDA:



EOB-DTPA is a derivative of DTPA. Hence, Gadoxetate Disodium is a derivative of Gd-DTPA as I am showing in the following comparison:

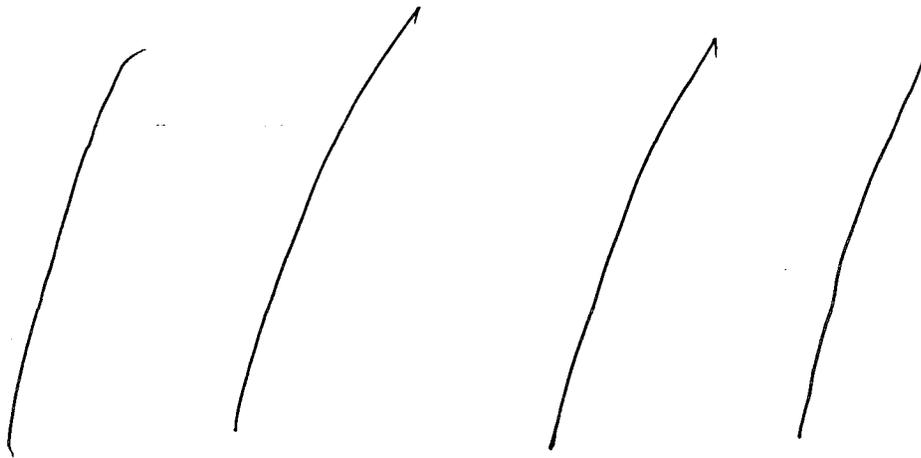


Gd-EOB-DTPA  
(Gadoxetate Disodium)



Gd-DTPA

When  $\text{Na}^+$  counterion in the above structure (far right) is replaced with meglumine, the result is the approved Magnevist (June 2, 1988). The gadolinium complex core unit is the same in Primovist and Magnevist, that of "Gd-DTPA." Where the structure in Gd-EOB-DTPA (Primovist) differs from the complex in Magnevist is in the attachment of the pendant ethoxybenzyl group to Gd-DTPA, replacing a methylene hydrogen of one of the ethylene bridges. That is shown in the above comparison of the two structures. The ethoxybenzyl group imparts greater lipophilicity to Primovist compared to that of Gd-DTPA complex in Magnevist, resulting in weaker protein binding, which in turn is expected to allow Gd-EOB-DTPA to enter the hepatocytes through membrane bound carriers. Bayer concludes that this result improves the detection of liver lesions by increasing the difference in signal intensity between normal liver parenchyma and liver lesion, thus combining "the features of an extracellular contrast agent and a hepatocyte-specific agent."

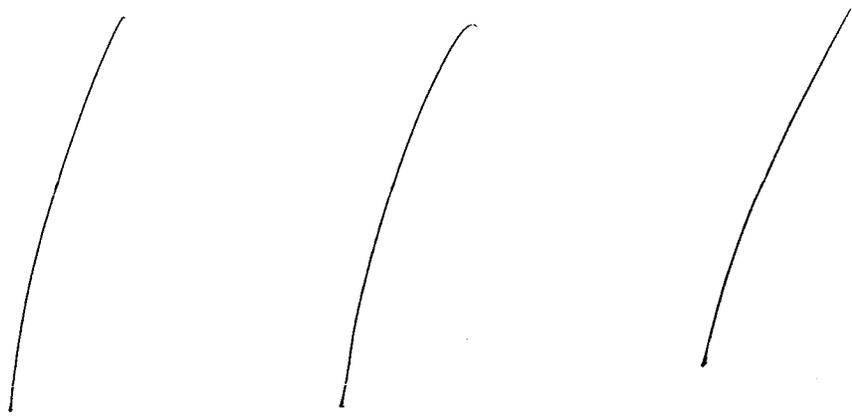


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Draft Labeling

Deliberative Process



**C. Comments for 74-Day Letter**

The CMC information is provided in electronic CTD format, and appears to be complete. It is well organized and legible, and reports (methods validation, stability, etc.) are present.

The following Fileability Summary provides a synopsis of the elements that need to be present for a decision of fileability from the standpoint of CMC. At this time, there are no comments for a 74-day letter.

### Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		
13.	Has the applicant provided a method validation package?	X		
14.	Is a separate microbiological section included?	X		

CGMP Inspections Required			
Facility	For:	Address	
Bayer Healthcare	/ /	Bayer Schering Pharma AG Ernst Schering Str. 14 D-59192 Bergkamen, Germany	Manufacture Testing Release
Bayer Healthcare	Drug Product	Bayer Schering Pharma AG Müllerstrasse 170-178 D-13353 Berlin, Germany Federal Republic of Germany	Mnufacture Testing Release

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
	Bayer Healthcare Pharmaceuticals, Montville, NJ 07045-1000		X		
			X		

Consults To Be Initiated	
Item	Consult To
Microbiology (closure integrity testing; )	Microbiology Staff

Pharmaceutical Assessment Lead:  
Branch Chief:

Eldon E. Leutzinger, Ph.D.  
Ravi Harapanhalli, Ph.D.

Date: 08/21/2007  
Date:

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Eldon Leutzinger  
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8/28/2007 11:36:39 AM  
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