CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

CHEMISTRY REVIEW(S)

NDA 21-357

Multihance (gadobenate dimeglumine) Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Bracco Diagnostics Inc.

Indication: Magnetic resonance imaging contrast agent for CNS in adults

Presentation: Clear colorless solution in a single use vial 529 mg/mL in 5, 10, 15, 20 mL

EER Status: Acceptable 22-FEB-2004

Consults: DMETS – MultiHance acceptable – 19-NOV-2004
DDMAC - unacceptable
Microbiology – recommended for AP – 5-JAN-2001

Multihance (gadobenate dimeglumine) is a gadolinium complex of a derivatized EDTA [BOPTA](as the meglumine salt). It is an NME.

Multihance is indicated for intravenous use in magnetic resonance imaging (MRI) of the Central Nervous System in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

Labeling was reviewed and was found acceptable with the minor revision in the dosage and administration section to indicate that administration "...as a rapid bolus intravenous injection." Note that the Tradename in the most recent labeling (immediate container and PI) is "Multihance", in contrast to all previous versions which was "MultiHance". This tradename was accepted by DMETS but was rejected by DDMAC because it suggests that the product has some unique effectiveness or composition – the Division has rejected this concern and accepts the proposed tradename. Immediate container labels are acceptable.

Due to handling difficulties of the gadobenate dimeglumine drug substance the

Manufacturing controls are considered adequate, as

are the finished product specifications and test procedures (Note – the final review dated 26-FEB-2004 found all deficiency comments adequately responded to – these deficiencies largely related to the finished product release and stability tests, acceptance criteria and procedures and methods validation).

Stability data through 24 months is acceptable to support a 24 month expiry,

Over-All Conclusion
From a CMC perspective an approval action is recommended.

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
11/23/04 03:11:25 PM
CHEMIST

Review of Chemistry, Manufacturing, and Controls

NDA 21–357

MultiHance®

Bracco Diagnostics Inc.

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Chemistry II – HFD-820

for

Clinical Review Division: HFD-160

Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21–357

2. **REVIEW #** 2

3. **REVIEW DATE:** 25–FEB–2004

4. **REVIEWER:** David A. Place, PhD, HFD-820

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	28–FEB–2001

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Resubmission	10–OCT–2003
Amendment	16–JAN–2004

7. **NAME & ADDRESS OF APPLICANT:**

Name:.	Bracco Diagnostics Inc
Address:	PO Box 5225, Princeton, NJ 06134
Representative:	Melanie Benson mbenson@diag.bracco.com
Telephone:	(609) 514–2254

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: MultiHance®
b) Non-Proprietary Name: Gadobenate dimeglumine
c) Code Name/# (ONDC only): B19036/7
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type: 1
- Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** Not Applicable to NDAs

10. **PHARMACOLOLGICAL CATEGORY/INDICATION:** Magnetic Resonance Imaging Contrast Agent: Indicated for the detection, during magnetic resonance imaging in adults.

11. **DOSAGE FORM:** Sterile solution for injection, presented in 5, 10, 15, and 20 mL vials.

12. **STRENGTH/POTENCY:** 0.5 M, equiv. to 529 mg gadobenate dimeglumine/mL

13. **ROUTE OF ADMINISTRATION:** IV

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 AND WEIGHT:

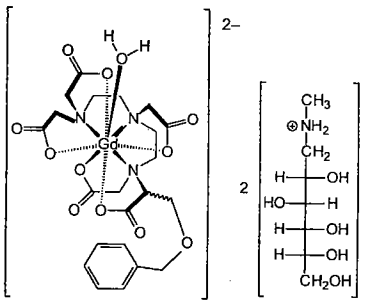
Chemical Name(s): (4*RS*)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolinate(2-) dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

Or GdBOTPA dimeglumine

CAS Registry No. 127000-20-8

Molecular Formula: $C_{36}H_{62}GdN_5O_{21}$ (anhydrous)

Molecular Weight: 1058.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	Comments
[redacted]	III	[redacted]	[redacted]	3	Adequate	9-SEP-2000	N/A
				3	Adequate	2-APR-1997	N/A
				3	Adequate	27-NOV-2001	N/A

a 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")

b 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
N/A		

Patent: US patent No. 4,916,246

Exclusivity: Five years requested.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	24-FEB-2004	OC
Pharm/Tox			
Biopharm			
LNC	USAN Approved	N/A	
Methods Validation	To be requested		
OPDRA	Acceptable		
EA	Categorical Exclusion Satisfactory	25-JAN-2002	David Place
Microbiology	Acceptable	05-JAN-2001	Stephen Langille

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): *Not Applicable*

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

Chemistry Review for NDA 21–357

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The chemistry section is recommended for "Approval"

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

II. Summary of Chemistry Assessments

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

MultiHance® is a sterile/pyrogen–free solution for intravenous injection containing 0.5 M gadobenate dimeglumine, to be used as a contrast agent for magnetic resonance imaging (MRI). In it's single–use presentation, the product will be available in four vial fill sizes: 5, 20, 15, and 20mL.

Gadobenate dimeglumine (USAN)

The methods used for the manufacture of gadobenate dimeglumine also are designed to minimize process impurities and related substances. Temperature and duration of the reaction are carefully controlled to this end. In–process controls during production of MultiHance are also utilized, and the methods adequately assay the purity of the preparation prior to final dosage form packaging.

The drug product is tested at release for the following specifications: appearance ,visible particles, particulate matter, pH, free gadolinium, ——— , integrity testing, identity (TLC), identity (HPLC), identity (IR), impurities (——— HPLC), gadobenate (gadobenic acid, HPLC), meglumine, sterility, and endotoxins. All specifications are adequate.

Stability specifications are the same as those at time of release. The primary stability batches stored at 25°/60% out to 24 months continue to be well within specifications. ———

In this resubmission, the sponsor submits responses to the approvable letter of May 24, 2002. The sponsor adequately responds to the identified deficiencies, primarily in the Methods Validation section.

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

Single–dose vials of MultiHance containing 0.5 M gadobenate dimeglumine will be administered as an IV bolus prior to performing MRI scanning of the patient. In adults, a — dose of 0.1 mmol/Kg

C. Basis for Approvability or Not-Approval Recommendation

The resubmission resolves minor deficiencies and errors, primarily in the Methods Validation section. Therefore, the application is recommended for approval.

III. Administrative

A. Reviewer's Signature

Chemist	David A. Place, PhD	_____	Date: 25–FEB–2004

B. Endorsement Block Same date as draft review

Chemistry Team Leader	Eldon Leutzinger, PhD	_____	Date:
Project Manager	James Moore, MPh	_____	Date:

C.

cc: Orig. NDA 21–357
~~HFD–160/Division~~ File
HFD–820/ChemDivDir/EDuffy
HFD–160/MO/RRaman/RYaes
HFD–160/Pharm/TKokate
HFD–160/ActDivDir/SLoewke

CH-1

12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21357/000	Action Goal:	
Stamp:	27-APR-2001	District Goal:	14-FEB-2004
Regulatory Due:	14-APR-2004	Brand Name:	MULTIHANCE(GADOBENATE
Applicant:	BRACCO	Estab. Name:	DIMEGLUMINE INJ)
	5225	Generic Name:	GADOBENATE DIMEGLUMINE
	PRINCETON, NJ 08543		INJ
Priority:	1S	Dosage Form:	(INJECTION)
Org Code:	160	Strength:	529 MG/ML

Application Comment: THE CHEMISTRY REVIEWER WOULD APPRECIATE THE OPPORTUNITY TO ACCOMPANY THE INSPECTION TEAM TO BOTH OF THESE SITES. (on 15-MAY-2001 by D. PLACE (HFD-160) 301-827-7510)

FDA Contacts:	J. MOORE	(HFD-160)	301-827-7510 , Project Manager
	D. PLACE	(HFD-160)	301-827-7510 , Review Chemist
	E. LEUTZINGER	(HFD-160)	301-827-7510 , Team Leader

Overall Recommendation: ACCEPTABLE on 24-FEB-2004by J. D AMBROGIO(HFD-322)301-827-9049

ACCEPTABLE on 20-FEB-2002by GARCIAM

Establishment: CFN 9611622 FEI 3002806615

ALTANA PHARMA

ROBERT BOSCH STRASSE 8

SINGER, , GM D-78224

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVT OAI Status: NONE

Lab. Comment: THIS SITE WAS ALSO LISTED IN THE NDA AS ——— (on 15-MA
J01 by D.

PLACE (HFD-160) 301-827-7510)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC PLACED	21-MAY-2001			
SUBMITTED TO DO EGASM	22-MAY-2001	PS		
ASSIGNED INSPECTION T EGASM	22-MAY-2001	PS		
INSPECTION SCHEDULED IRIVERA	02-OCT-2001		16-OCT-2001	
INSPECTION PERFORMED IRIVERA	17-OCT-2001		17-OCT-2001	
DO RECOMMENDATION GARCIAM	17-JAN-2002			ACCEPTABLE INSPECTION

OC RECOMMENDATION GARCIAM	17-JAN-2002		ACCEPTABLE
			DISTRICT RECOMMENDATI
SUBMITTED TO OC PLACED	23-FEB-2004		
SUBMITTED TO DO DAMBROGIOJ	23-FEB-2004	10D	
DO RECOMMENDATION ADAMSS	24-FEB-2004		ACCEPTABLE
			BASED ON FILE REVIEW
OC RECOMMENDATION DAMBROGIOJ	24-FEB-2004		ACCEPTABLE
			DISTRICT RECOMMENDATI

ON

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN 9611860 FEI 3002806807

BRACCO IMAGING SPA

VIA PER CERIANO

LAGHETTO, MILAN, IT

DMF No: AADA:

sponsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

EMilestone Name / Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC PLACED	21-MAY-2001			
SUBMITTED TO DO EGASM	22-MAY-2001	PS		
ASSIGNED INSPECTION T EGASM	22-MAY-2001	PS		
SPECTION SCHEDULED IRIVERA	18-DEC-2001		30-JAN-2002	
INSPECTION PERFORMED IRIVERA	30-JAN-2002		30-JAN-2002	
DO RECOMMENDATION GARCIAM	20-FEB-2002			ACCEPTABLE

		INSPECTION
OC RECOMMENDATION GARCIAM	20-FEB-2002	ACCEPTABLE
		DISTRICT RECOMMENDATI ON
SUBMITTED TO OC PLACED	23-FEB-2004	
OC RECOMMENDATION DAMBROGIOJ	23-FEB-2004	ACCEPTABLE
		BASED ON PROFILE

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/s/

David Place
2/25/04 10:25:06 AM
CHEMIST

Eldon Leutzinger
2/25/04 10:33:27 AM
CHEMIST
I concur with the conclusions and recommendation for chemistry.

NDA 21-357

MultiHance (gadobenate dimeglumine) Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Bracco Diagnostics Inc.

Indication: Magnetic resonance imaging contrast agent for CNS in adults .

Presentation: Clear colorless solution in a single use vial 529 mg/mL in 5, 10, 15, 20 mL

EER Status: Acceptable 20-FEB-2002

Consults: OPDRA – MultiHance acceptable
Microbiology – recommended for AP

MultiHance (gadobenate dimeglumine) is a gadolinium complex of a derivitized EDTA [BOPTA](as the meglumine salt) which increases the complex lipophilicity and therefore improves hepatic uptake.

The **Drug Substance** is manufactured by Bracco Imaging, SpA, Milan Italy – acceptable GMP inspection onfirmed 2/20/02. The manufacture of the BOPTA complex and purification is performed followed by complexation with gadolinium oxide, salt formation and without isolation, drug product manufacture. The synthetic method can utillize several methods, all of which have been demonstratwed to be equivalent. The impurity profile is well defined and controlled.

The **Drug Product** formulation is simply the drug substance in water for injection. Product is manufactured at , acceptable GMPs 2/20/02. Batch sizes are , and adequate manufacturing controls are in place. . Sterility assurance has been demonstrated. The packaging components were found acceptable (DMF). The specification is approvable pending resolution of several issues. Several issues remain unresolved regarding the methods validation.

Production scale batched were placed on stability through 24 months under ICH room temperature,
An expiry of 24 months is granted.

Labeling was reviewed and was found acceptable with the exception of 2 minor points.

Over-All Conclusion
From a CMC perspective an approvable action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
2/21/02 05:00:51 PM
CHEMIST

Review of Chemistry, Manufacturing, and Controls

NDA 21–357

MultiHance®

Bracco Diagnostics Inc.

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Chemistry II – HFD-820

for

Clinical Review Division: HFD-160

Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21–357

2. REVIEW # 1

3. REVIEW DATE: 25–JAN–2002

4. REVIEWER: David A. Place, PhD, HFD-820

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28–FEB–2001

7. NAME & ADDRESS OF APPLICANT:

Name:.	Bracco Diagnostics Inc
Address:	PO Box 5225, Princeton, NJ 06134
Representative:	Melanie Benson mbenson@diag.bracco.com
Telephone:	(609) 514–2254

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MultiHance®
b) Non-Proprietary Name: Gadobenate dimeglumine
c) Code Name/# (ONDC only): B19036/7
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable to NDAs

10. PHARMACOLOLGICAL CATEGORY/INDICATION: Magnetic Resonance Imaging Contrast Agent: Indicated for the detection,
during magnetic resonance imaging in adults.

11. DOSAGE FORM: Sterile solution for injection, presented in 5, 10, 15, and 20 mL vials.

12. STRENGTH/POTENCY: 0.5 M, equiv. to 529 mg gadobenate dimeglumine/mL

13. ROUTE OF ADMINISTRATION: IV

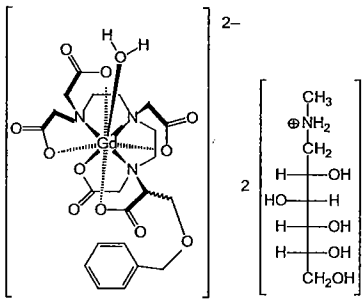
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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:

Chemical Name(s): (4*RS*)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolinate(2-) dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)
Or GdBOTPA dimeglumine
CAS Registry No. 127000-20-8
Molecular Formula: $C_{36}H_{62}GdN_5O_{21}$ (anhydrous)
Molecular Weight: 1058. —



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	Comments
—	III	[redacted]		3	Adequate	9-SEP-2000	N/A
				3	Adequate	2-APR-1997	N/A
				3	Adequate	27-NOV-2001	N/A

a 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")

b 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
N/A		

Patent: US patent No. 4,916,246

Exclusivity: Five years requested.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm			
LNC	USAN Approved	N/A	
Methods Validation	To be requested after resubmission		
OPDRA	Acceptable		
EA	Categorical Exclusion Satisfactory		David Place
Microbiology	Acceptable	05-JAN-2001	Stephen Langille

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): *Not Applicable*

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

Appears This Way
On Original

Chemistry Review for NDA 21–357

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is "Approvable" pending resolution of various deficiencies in the drug product testing and Methods Validation sections. See Deficiency Letter to Applicant.

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

II. Summary of Chemistry Assessments

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

MultiHance® is a sterile/pyrogen–free solution for intravenous injection containing 0.5 M gadobenate dimeglumine, to be used as a contrast agent for magnetic resonance imaging (MRI). In it's single–use presentation, the product will be available in four vial fill sizes: 5, 20, 15, and 20mL.

Gadobenate dimeglumine (USAN)

The methods used for the manufacture of gadobenate dimeglumine also are designed to minimize process impurities and related substances. Temperature and duration of the reaction are carefully controlled to this end. In–process controls during production of MultiHance are also utilized, and the methods adequately assay the purity of the preparation prior to final dosage form packaging.

The drug product is tested at release for the following specifications: appearance ,visible particles, particulate matter, pH, free gadolinium , integrity testing, identity (TLC), identity (HPLC), identity (IR), impurities (HPLC), gadobenate (gadobenic acid, HPLC), meglumine, sterility, and endotoxins. The only release specification that appears anomalous is that for pH (6.5–7.5), which does not compare favorably to the in–process specification of . All other specifications are adequate.

Stability specifications are the same as those at time of release. The primary stability batches stored at 25°/60% out to 24 months continue to be well within specifications.

There are some inconsistencies in this section with those corresponding tests in earlier sections of the NDA that will require clarification or correction.

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

Single–dose vials of MultiHance containing 0.5 M gadobenate dimeglumine will be administered as an IV bolus prior to performing MRI scanning of the patient. In adults, a dose of 0.1 mmol/Kg

C. Basis for Approvability or Not-Approval Recommendation

The submission contains minor deficiencies and errors, primarily in the Methods Validation section. Therefore, the application is approvable.

III. Administrative

A. Reviewer's Signature

Chemist	David A. Place, PhD	/S/	Date: 25-JAN-2002

B. Endorsement Block Same date as draft review

Chemistry Team Leader	Eldon Leutzinger, PhD		Date:
Project Manager	James Moore, MPh		Date:

C.

cc: Orig. NDA 21–357
HFD–160/Division File
HFD–820/ChemDivDir/EDuffy
HFD–160/MO/RRaman/RYaes
HFD–160/Pharm/TKokate
HFD–160/DivDir/PLove

CH-2

51 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

David Place
1/25/02 03:46:03 PM
CHEMIST
Recommended as approvable

Eldon Leutzinger
1/25/02 03:54:06 PM
CHEMIST
I concur with the conclusions and recommendations arrived at in the review of NDA 21-357.