CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-066

CHEMISTRY REVIEW(S)

OMNISCAN (gadodiamide) Injection – Pharmacy Bulk Package

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 22-066

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-066

2. REVIEW # 1

3. REVIEW DATE: April 20, 2007

4. REVIEWER: Eldon E. Leutzinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-JUL-2006
Amendment N-000-BL	06-AUG-2006
Amendment N-000-BI	06-OCT-2006
Amendment N-000-BL	06-NOV-2006
Amendment N-000-BC	06-NOV-2006
Amendment N-000-BC	06-DEC -2006
Amendment N-000*	
Amendment N-000*	

* Responses from GE to CMC labeling recommendations, EMAIL dated 17-APR-2007
** Revised Draft Label for container from GE, EMAIL dated 19-APR-2007
Hardcopies of these EMAILS have not yet been submitted.

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: GE Healthcare

Address: 101 Carnegie Center

Representative: Princeton, New Jersey 08540

Telephone: 609-514-6472 (Michael Barbush)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Gadodiamide Injection-Pharmacy Bulk Package
b) Non-Proprietary Name (USAN): Gadodiamide
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new dosage form)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Contrast for MRI

11. DOSAGE FORM: Solution, Pharmacy Bulk Package

12. STRENGTH/POTENCY: 0.5 mmol/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

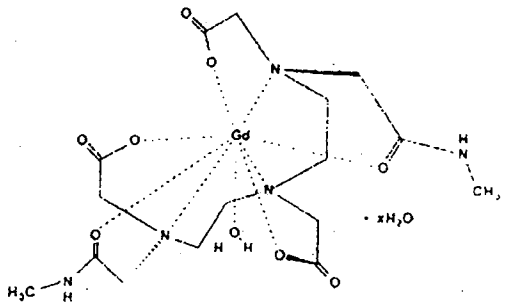
_____SPOTS product – Form Completed

___X_Not a SPOTS product

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

Chemical Name: Gadolinium(III)diethylenetriaminepentaacetic acid bismethylamide
CAS Registry No: 131410-48-5
Molecular Weight: 573.66
Molecular Structure: See next page

Molecular Structure Contd.:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3	Adequate	2/26/2004	

[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
None		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		A decision from Office of Compliance is pending as of 4/19/2007
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DEMETS	Recommendations for changes to labels	3/22/2007	Todd Bridges, R.Ph.
EA	Acceptable	3/30/2007	Eldon E. Leutzinger, Ph.D.
Microbiology	Recommended for approval; See Microbiology Review	4/10/2007	Robert Mello, 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:

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-683

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval, pending a satisfactory CGMP recommendation for the GE manufacturing facilities.

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)

Omniscan Injection (Drug Product) is a clear, colorless to slightly yellow aqueous solution for injection, and is presented in fill sizes of 50 mL in 50 mL bottles, 100 mL fill in 100 mL bottles. The active ingredient is Gadodiamide. Other ingredients include Caldiamide sodium, sodium hydroxide and/or hydrochloric acid for pH adjustment, and WFI. [redacted] The chemical name of Gadodiamide (Drug Substance) is [5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3-)]gadolinium. [redacted] The manufacture and controls for Gadodiamide are described in the approved NDA 20-123. See Section S.1.2 for the structure of Gadodiamide drug substance. Omniscan Injection is packaged in [redacted] bottles with rubber stopper held in place with a tamper evident screw cap.

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

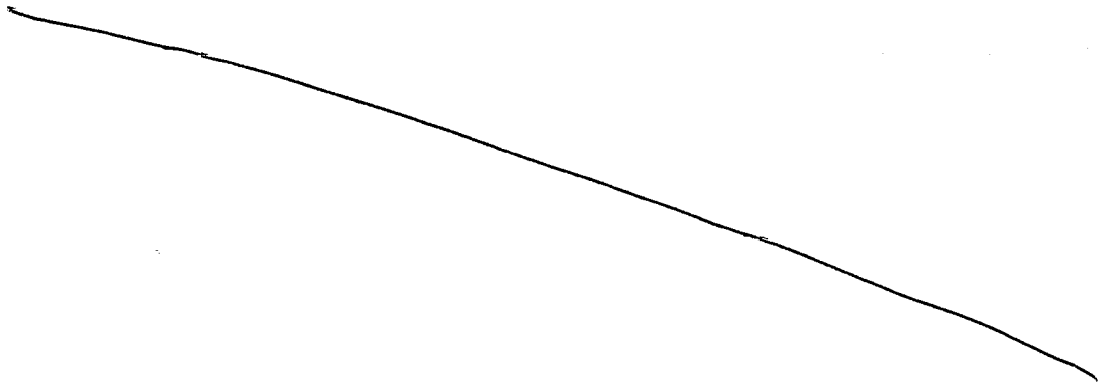
The product (Omniscan Injection, Pharmacy Bulk Package) is a container of Omniscan Injection for parenteral use that contains many single doses. It is Not for Direct Infusion. The closure is to be penetrated only once using a suitable transfer device and aseptic technique. Once penetrated, contents are withdrawn without delay. If delay is unavoidable the fluid transfer is to be completed as soon as possible within a maximum time of 8 hours. The container is to be kept in the aseptic area and at room temperature, not to exceed 30^0C. Each individual dose immediately following withdrawal is to be used, and any portion of it not used is to be immediately discarded. Also, any Omniscan Injection remaining in the Pharmacy Bulk Package is to be discarded after 8 hours following penetration of the container closure. Omniscan is used for (1) visualizing lesions with abnormal vascularity in the brain, spine and associated tissues and (2) for facilitating the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space.

C. Basis for Approvability or Not-Approval Recommendation

(Basis for Approval).

The formulation of Omniscan Injection in the Pharmacy Bulk Package is exactly the same as that in the approved Omniscan Injection under NDA 20-123. Also, there are no changes in the manufacture of Gadodiamide, inactive ingredients or formulation of Omniscan Injection from that of the approved product under NDA 20-123. However, there is a change in the container / closure system on going to the Pharmacy Bulk Package (NDA 22-066). This change creates two consequences for consideration. The first of these concerns extractables that have potential for leaching from the polymer of the container into the product. In an initial extractables study under extreme conditions, inconceivable of occurrence under real circumstances, GE identified a number of extractable substances, an extractable profile of which is similar to that obtained for Omnipaque and Visipaque packaged in the same container / closure system and similar aqueous vehicle as Omniscan (NDA 22-066). The levels of these extractables were very low, and far below known toxicity levels in humans (ICH Q3C). Pharm/Tox assessments had been done on the previous products, the containers of which were manufactured from the same polymer; no issues were identified. Compatibility studies are currently in progress, an extension of those described in this submission, and will continue concurrent with the stability studies throughout the shelf-life of the product; this provides a good safeguard built into the controls for the product. None of the substances in the compatibility studies have shown any indication of growing with time. There are no issues for extractable substances that stand in the way of approval.

The second consideration is vapor permeation, which occurs through the rubber stopper / closure used in the Pharmacy Bulk Package. Vapor permeation results in a relatively small decrease in extractable volume and a small increase in Gadodiamide concentration with passage of time during storage. This has also been observed in the Pharmacy Bulk Packages for Omnipaque and Visipaque, both with 36 months of expiration dating. GE performed vapor permeation studies and developed a model that characterizes vapor permeation in the containers (50 mL and 100 mL) for Omniscan Injection / Pharmacy Bulk Package, very similar as that for Omnipaque and Visipaque. Based on this model, they estimate the expiration dating period to be 36 months. Their model is derived on the basis of sound scientific principles, and has a proven record for Omnipaque and Visipaque. As well, vapor permeation through rubber, plastics and laminates is a well-known phenomenon and has been the subject of extensive studies since the mid 1930's.



Based on the history of proven stability of Omniscan Injection, the vapor permeation studies, and the sameness of the container / closure system with Omnipaque and Visipaque in which vapor permeation was also observed, there is no compelling reason in my opinion to expect Omniscan Injection Pharmacy Bulk Package to not meet the estimated expiration dating of 36 months. They have a satisfactory Stability Program and Stability Commitment. Hence, it is my opinion that NDA 22-066 can be approved with their proposed 36 months of expiration dating.

A number of issues for CMC regarding labeling have been identified, primarily with making certain items more prominent on the bottle and shipper label, and comments were conveyed to GE on April 5, 2007. The list of these comments is in Section II.A. of this review. We received GE's responses, and they have agreed to all of the CMC recommendations. GE also understood our issue for designating this presentation as a [redacted] and has agreed to delete this term from the label as an interim measure, pending guidance from the division on what future terminology would be acceptable to the Agency. They submitted a Revised Draft label (April 20, 2007) that includes all of our recommendations. At this point in time, all of the CMC issues for labeling have been resolved. An inspection of GE's Ireland and Norway facilities was scheduled for January 29, 2007. Although these inspections have been performed, as of the date of this review an official recommendation on the CGMP status of these facilities has not yet been rendered. Hence, the CMC recommendation for NDA 22-066 is approval, pending a satisfactory outcome of the CGMP inspections.

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 / Tiffany Brown, Pharm.D.
ONDQA Project Manager Name / Karl Stiller, Pharm.D.

66 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Eldon Leutzinger
4/20/2007 03:03:24 PM
CHEMIST

Ravi Harapanhalli
4/23/2007 04:00:28 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22066/000 Sponsor: GE HEALTHCARE

Org Code : 160 101 CARNEGIE CENTER

Priority : PRINCETON, NJ 085406231

Stamp Date : 07-JUL-2006 Brand Name : OMNISCAN INJ

PDUFA Date : 07-MAY-2007 Estab. Name:

Action Goal : Generic Name: GADODIAMIDE

District Goal: 08-MAR-2007 Dosage Form: (INJECTION)

Strength : 287 MGI/ML

FDA Contacts: K. STILLER Project Manager (HFD-800) 301-796-1993

E. LEUTZINGER Review Chemist 301-796-1399

Overall Recommendation: ACCEPTABLE on 23-APR-2007by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : 9610480 FEI : 3002807778

GE HEALTHCARE

LINDESNES PLANT RAMSIANGVAGEN

SPANGEREID, , NO

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-APR-07

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9710691 FEI : 3003495327

GE HEALTHCARE IRELAND

IDA BUSINESS PARK

CARRIGTOHILL, COUNTY CORK, EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVT OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-APR-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

APPEARS THIS WAY ON ORIGINAL

METHODS VALIDATION

The section is not applicable for this application. Please see CMC review.

Application Integrity Policy (AIP)

The section is not applicable for this application.