CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

CHEMISTRY REVIEW(S)

AdreView
(Iobenguane I 123 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 22-290

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

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Chemistry Review Data Sheet

1. NDA 22-290

2. REVIEW # 1

3. REVIEW DATE: 09/05/2008

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	20-MAR-2008
Amendment N-000-BC	21-APR-2008
Amendment N-000-BC	28-APR-2008
Amendment N-000-BC	07-JUL-2008
Amendment N-000-BZ	16-JUL-2008
Amendment N-000-BC	28-JUL-2008
Amendment N-000-BC	08-AUG-2008
Amendment N-000-SU	19-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	GE Healthcare Corporation
Address:	101 Carnegie Center Princeton, NJ 08540
Representative:	Fred E. Longenecker U.S. Regulatory Site Head
Telephone:	1-609-514-6000

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AdreView (proposed)
b) Non-Proprietary (Established Name): Iobenguane I 123 Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Diagnostic radiopharmaceutical

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 2 mCi/mL

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: X Rx ___OTC

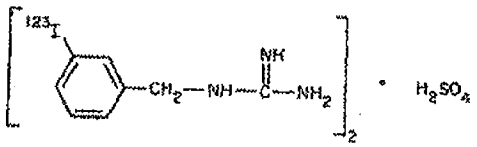
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Chemical Name: m-Iodo-^{123}I-benzylguanidine sulfate (2:1)[1]
CAS Registry No: 139755-80-9
GE code: [^{123}I]MIBG
Molecular Formula: $(C_8H_{10}{}^{123}IN_3)_2 \cdot H_2SO_4$[1]
Molecular Weight: 640.448[2]
Molecular Structure: See next review page[3]



(1) The compound is a salt, and it is the "sulfate" that is recognized in both USP and USAN. As a salt, the ratio of MIBG to H_2SO_4 is 2:1 (seen in the structure as shown in USP and USAN). This will be discussed at further length under Characterization (S.3.1).
(2) This molecular weight reflects the 2:1 ratio of the salt.
(3) The above indicated structure is that officially recognized in the USP and USAN. This structure will be discussed at further length under S.3.1.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	07/24/2008	None
	II			1	Adequate	07/23/2008	None
	III			4	-------	------	None
	V			4	--------	-------	None

b(4)

[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)

(1) The rubber stopper is described in the NDA. What is pertinent to this rubber stopper, per its use in NDA 22-290, is a report of a extractables / leachables by ——— as requested by GE. This report contains b(4)

the results of a comprehensive study of an impurity leached from the stopper and found in the [^{123}I]MIBG product. This is discussed in detail later in the review.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,669	Iobenguane I 123 Injection

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	June 26, 2008	Office of Compliance
Pharm/Tox	Pending		Siham, Biade, Ph.D.
Biopharm	Pending		Christy John, Ph.D.
Microbiology	Approval	9/3/2008	Robert Mello, Ph.D.
LNC	N/A		
Methods Validation	N/A		
DMETS	Tradename acceptable	August 4, 2008	
EA	Acceptable	July 28, 2008	Eldon E. Leutzinger, 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:

III. Administrative

A. Reviewer's Signature

Eldon E. Leutzinger, Ph.D.

B. Endorsement Block

CMC Reviewer's Name / Eldon E. Leutzinger, PhD.
Pharmaceutical Assessment Lead, Branch V
Division of Pre-Marketing Assessment III & Manufacturing Science

CMC / Division Director / Richard T. Lostritto, Ph.D.
Division of Pre-Marketing Assessment III & Manufacturing Science

C. CC Block

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

The Chemistry Review for NDA 22-090

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-290 is recommended for APPROVAL from a Chemistry, Manufacturing and Controls perspective.

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

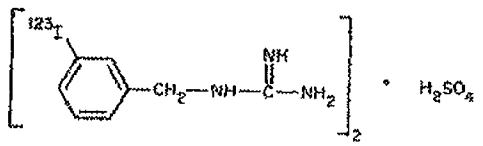
N/A

II. Summary of Chemistry Assessments

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

The Drug Product is a sterile aqueous solution, each mL of which contains 74 MBq (2 mCi) of Iobenguane sulfate I 123, 0.08 mg of Iobenguane sulfate, 23.0 mg of sodium dihydrogen phosphate dehydrate, 2.8 mg of disodium hydrogen phosphate dehydrate and 10.3 mg (1%) of benzyl alcohol at pH 5.0 – 6.5. It is packaged as a single dose of 5.0 mL (370 MBq, 10 mCi) in a 10 mL glass vial closed [redacted] The function of benzyl alcohol [redacted] b(4)

Iobenguane sulfate I 123 (Drug Substance) is (m-iodo-^{123}I-benzylguanidine) sulfate, the sulfate salt of m-iodo-^{123}I-benzylguanidine and sulfuric acid in a ratio of 2:1, respectively. The Drug Substance has the following structure:



[redacted] ^{123}I is a pure gamma emitter, the energy of the major photopeak being 158 KeV (83%). Its half-life is 13.2 hours, and decays by electron capture to ^{123}Te. [redacted] b(4)

[redacted] The Drug Product is relatively stable, and is stored at room temperature, in contrast to [^{131}I]MIBG sulfate that must be stored frozen; the latter has a gamma emission of 364 KeV and a beta (negatron) emission of 806 KeV. Iobenguane I 123 Injection has an expiration dating period of 36 hours post reference, where the reference time is 24 hours after manufacture. b(4)

Drug Product is manufactured at Arlington Heights, ILL (GE) [redacted] b(4)

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

AdreView is a "ready to use" product, a sterile aqueous solution packaged in a 10 mL glass vial and sealed with [redacted] It is packaged as a single 5.0 mL dose, and contains 370 MBq (10 mCi) of ^{123}I radioactivity, as (m-iodo-^{123}I-benzylguanidine)sulfate. The product is stored at room temperature and is stable through an expiration dating period of 36 hours post reference; the reference time is 24 hours after manufacture. Iobenguane I 123 Injection is indicated for detection of primary or metastatic pheochromocytomas and neuroblastomas. b(4)

C. Basis for Approvability or Not-Approval Recommendation

(Basis for Approval).

AdreView is manufactured by GE Healthcare at Arlington Heights, ILL. This facility is CGMP compliant, receiving an acceptable inspection status on June 26, 2008 by the Office of Compliance. All CMC issues raised during the NDA review have been satisfactorily resolved. There are no remaining CMC issues. All labeling issues from a CMC standpoint have also been resolved.

Currently, there are several methods used in the production of [^{123}I]MIBG sulfate, but none that are standardized to produce product with a consistent chemical and radiochemical purity profile. This has been left to individual radiopharmacies of widely differing experience and skills in production of the product. The manufacturing process employed by GE represents a significant improvement over traditional methods. The approval of NDA 22-290 will make available a commercial product of consistent purity and quality, and thus fulfill a need for a standardized product that can deliver reproducible performance of this important and widely used diagnostic radiopharmaceutical product.

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Eldon Leutzinger
9/5/2008 02:07:12 PM
CHEMIST

Richard Lostritto
9/10/2008 03:49:05 PM
CHEMIST

Initial Quality Assessment (IQA)
Branch V

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

OND Division: DMIHP
NDA: 22-290
Applicant: GE Healthcare
Stamp Date: March 21, 2008
PDUFA Date: TBD (currently, under consideration for priority review)
Trademark: AdreView
Established Name: Iobenguane I 123 Injection
Dosage Form: Sterile solution
Route of Administration: IV injection
Indication: Imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas

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

	YES	NO
ONDQA Fileability:	X	
Comments for 74-Day Letter		X (not at this time)

Summary and Critical Issue

A. Summary

The drug product (Iobenguane I 123 Injection), [^{123}I]MIBG, with proposed tradename AdreView, consists of meta-[^{123}I] iodobenzylguanidine hemisulfate in aqueous solution with inactive ingredients and [redacted] Each mL of drug product contains [redacted] 23 mg sodium dihydrogen phosphate dehydrate, 2.8 mg disodium hydrogen phosphate dehydrate, 1% benzyl alcohol and at pH of 5.0 – 6.5. Product is supplied in a 10 mL [redacted] glass vial sealed with a closure [redacted] Radioactivity concentration is 74 MBq / mL (2 miCi / mL). Benzyl alcohol serves to [redacted]

b(4)

[^{123}I]MIBG drug product has been used for many years in research and clinical imaging of neuroendocrine tumors. It is not approved in the U.S., but is approved in Europe. Although this product is produced in many locations throughout the U.S., many of which are commercial or institutional radiopharmacies, it is produced by any number of methods not necessarily standardized to any significant extent.

There is a USP monograph for Iobenguane I 123 Injection, [^{123}I]MIBG, which is the current standard for purity and quality of the product. However, as with all USP monographs, the method of production is not specified. [redacted] b(4)

[redacted] b(4)

[redacted] b(4)

There is a sister product approved in the U.S. (Iobenguane Sulfate I 131 Injection), [^{131}I]MIBG , by (CIS-US), approved March 24, 1994 (NDA[redacted]. The drug substance in both the approved product and the subject product of this NDA possess the same chemical entity. However, the radiochemical entities differ by the isotope of iodine (^{131}I vs. ^{123}I), meta-[^{131}I] iodobenzylguanidine hemisulfate vs. meta- [^{123}I] iodobenzylguanidine hemisulfate (NDA 22-290). In accordance to FDA's Drug and Application Classification system, [^{123}I]MIBG will fall into the chemical classification of an NME (Type 1), where there is a change in the isotope (from ^{131}I to ^{123}I). The full statement from the Classification document reads as follows: b(4)

"An active ingredient in a radiopharmaceutical (or radioactive drug) in which the active moiety has not been approved by the FDA or marketed in the United States. In addition, a change in the isotope from a stable isotope to a radioactive isotope or from one radioactive isotope to another (e.g., ^{131}I to ^{123}I), resulting in an active moiety with different physicochemical characteristics (i.e., nuclear and physical properties) that has never been approved by the FDA or marketed in the United States is considered an NME."

[redacted] b(4)

7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Eldon Leutzinger
5/2/2008 09:58:31 AM
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Ravi Harapanhalli
5/8/2008 11:42:41 AM
CHEMIST
Need to initiate a microbiology consult