

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203137Orig1s000

CHEMISTRY REVIEW(S)

NDA 203137

Vizamyl (Flumetamol F 18) Injection
5 mCi (185 MBq)/10 mL
GE Healthcare
Princeton NJ

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Indication:

Vizamyl is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations (1).

Limitations of Use:

A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder

Safety and effectiveness of Vizamyl have not been established for:

Predicting development of dementia or other neurological condition

Presentations: The drug product is manufactured as 10 or 30 mL multidose vial presentations containing 150 MBq (4.05 mCi) at the reference date and time. Unit doses are prepared in the radiopharmacy at 185 mBq (max volume 10 mL)

Consults

Biopharm Recommendation:	NA
Establishments Evaluation Report:	Acceptable 2-OCT-2013
Note that there are 8 Cardinal Health facilities recommended for approval	
EA -	Categorical exclusion per 21CFR25.31 granted
Statistics -	N/A
Methods Validation -	Not requested
Microbiology -	Acceptable 18-JUN-2013
Pharm Toxicology -	Acceptable 27-JUN-2013
DMEPA	Proprietary name OK 14-FEB-2013

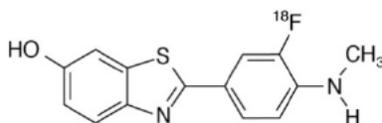
Original Submission: 26-OCT-2012

Post-Approval CMC Agreements: None

Drug Product Expiry: 10 hrs

Drug Substance

The cold drug substance precursor is prepared in a multistep process from commercially available starting materials. The flumetamol F18 is prepared in a the GE (b) (4)



Flumetamol F18

The drug substance is not isolated, and is directly formulated into the drug product. Impurities are controlled by the synthetic procedures. The cold precursor has a retest date of (b) (4) stored at -20C protected from light.

Conclusion: Drug substance is satisfactory

Drug product

Formulation of the in situ prepared flumetamol F18 with ethanol

(b) (4) polysorbate 80 (b) (4) NaCl (b) (4)

(b) (4) immediately following synthesis of the drug substance.

Product is filled into 10 or 30 mL multidose vials.

Specifications are acceptable

Tests	Analytical Methods	Acceptance Criteria ¹
Appearance	Visual Inspection	Clear, colorless to slightly yellow solution, practically free from visible particles.
Identification: [¹⁸ F] Flutemetamol by HPLC	HPLC with UV and Radioactivity detector	The principal peak in the radio chromatogram obtained with the test solution is similar in retention time as the principal peak obtained with flutemetamol reference solution.
Identification: Radionuclide by Half-life determination	Half life determination	105 to 115 min
Assay: Radioactive concentration (RAC) at end of synthesis	Ionization Chamber	NMT (b) (4)
Assay: Nominal ¹⁸ F activity	Ionization Chamber	(b) (4) % of 150 MBq/ml at the date and time stated on the label

<p>Microbiological tests Sterility² Bacterial endotoxins</p>	<p>Ph. Eur / USP Ph. Eur. / USP</p>	<p>Sterile █ (b) (4)</p>
<p>Radiopharmaceutical Purity Test Radiochemical purity Radiochemical Purity at release Greatest single unspecified impurity</p>	<p>HPLC with Radioactivity detector</p>	<p>NLT █(b) (4)% NLT █ % NMT █ %</p>
<p>Periodic quality indicator test Radionuclidic Purity³</p>	<p>Gamma ray spectroscopy</p>	<p>NLT █(b) (4)%</p>

Note that clinical trial supplies were prepared at 6 Cardinal Health sites.

Expiry 10 hrs.

Drug product is satisfactory

Labeling

Package insert and immediate and shield labeling is acceptable.

Overall Conclusion:

From the CMC point of view, the NDA may be approved.

Eric P. Duffy, Ph.D.
Director, Division III
ONDQA/CDER/FDA

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/s/

ERIC P DUFFY
10/23/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 16, 2013

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch VII, Division-III, ONDQA

Through: Danae Christodoulou, Ph.D.
Acting Branch Chief,
Branch VII, Division-III, ONDQA

Subject: NDA 203137, VizamyI™ (Flutemetamol F-18 Injection); Addendum to Chemistry Review # 1.

In chemistry review # 1, dated 28-Jun-2013, the application was recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided an acceptable form of compliance for manufacturing facility inspections is received, and acceptable final package insert and container closure labeling is received.

Additionally, following was recommended for phase 4 commitment:

“The method for the determination of Flutemetamol is not sufficiently specific in that the flutemetamol peak is not resolved from the specified impurity (b)(4). Hence flutemetamol is quantified along with impurity (b)(4) and reported as such. Provide commitment that within 1 year of the date of approval of this New Drug Application you will submit method(s) that can specifically quantify flutemetamol and the (b)(4) impurity. You will also amend the finished product specifications to provide for acceptance criteria for flutemetamol amount and for (b)(4) impurity amount.”

In the NDA amendment dated 17-Sep-2013 (submitted 19-Sep-2013), the company has committed that, “GE Healthcare commits to introduce separate specification parameters with accompanying method(s) for flutemetamol and the (b)(4) impurity within 1 year of the date of approval of NDA 203137”. The commitment is acceptable.

Additionally, CDER office of Compliance has recommended (EES report dated 02-Oct-2012) that the proposed manufacturing facilities are acceptable.

The revised labeling (insert and labels) have been submitted and are acceptable. The description section and the revised labels are appended to this memorandum.

Conclusion and recommendation: Since all the pending CMC related issues have been satisfactorily addressed, the application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RAVINDRA K KASLIWAL
10/16/2013

DANAE D CHRISTODOULOU
10/16/2013

I concur with the reviewer's conclusions and recommendation

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 203137/000
Code: 160
Priority: 1
Stamp Date: 26-OCT-2012
PDUFA Date: 26-OCT-2013
Action Goal:
District Goal: 26-MAY-2013

Sponsor: GE HEALTHCARE
 101 CARNEGIE CENTER
 PRINCETON, NJ 085406231
Brand Name: VIZAMYL
Estab. Name:
Generic Name: FLUTEMETAMOL (18F) INJECTION
Product Number; Dosage Form; Ingredient; Strengths
 001; SOLUTION, INJECTION; FLUTEMETAMOL F-18; 4.05mCi

FDA Contacts:	R. KASLIWAL	Prod Qual Reviewer		3017961386
	R. MELLO	Micro Reviewer	(HFD-805)	3017961574
	Y. LIU	Product Quality PM		3017961926
	S. THOMAS	Regulatory Project Mgr		3017961994
	E. LEUTZINGER	Team Leader		3017961399

Overall Recommendation:	ACCEPTABLE	on	(b) (4)	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on	01-MAY-2013	by EES_PROD	
	PENDING	on	01-MAY-2013	by EES_PROD	
	PENDING	on	01-MAY-2013	by EES_PROD	
	PENDING	on	07-JAN-2013	by EES_PROD	
	PENDING	on	07-JAN-2013	by EES_PROD	
	PENDING	on	07-JAN-2013	by EES_PROD	
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	PENDING	on	07-JAN-2013	by EES_PROD	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: CARDINAL HEALTH 414 LLC
FEI: 3008619510
PHOENIX, , UNITED STATES 850404820

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
 (b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: CARDINAL HEALTH 414 LLC (DENVER CO)
FEI: 3008212446
DENVER, , UNITED STATES 80238

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
 (b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1287289 FEI: 1287289
CARDINAL HEALTH 414, INC.

WOBURN, , UNITED STATES 018011757

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

(b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3003411150
CARDINAL HEALTH 414, INC.

COLTON, , UNITED STATES 92324

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

(b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: **CFN:** **FEI:** 3004010371
 CARDINAL HEALTH 414, LLC

DMF No: DALLAS, , UNITED STATES 752474933 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 [REDACTED] (b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 1717928 **FEI:** 1717928
 CARDINAL HEALTH 418, INC.

DMF No: AURORA, , UNITED STATES 800113378 **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: NO FURTHER EVALUATION

Milestone Date: 26-MAR-2013

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 3004056100
CARDINAL HEALTH, MSU P.E.T. SITE
EAST LANSING, , UNITED STATES 48824

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
 (b) (4)

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-FEB-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9610481 FEI: 3002807779
GE HEALTHCARE AS
NYCOVEIEN 2
OSLO, , NORWAY

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

NDA 203137

VIZAMYLTM Flutemetamol F 18 Injection

**GE Healthcare
101 Carnegie Center
Princeton NJ 08450, USA**

**Ravindra K. Kasliwal, Ph.D.
Division of Medical Imaging Products**

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Chemistry Review Data Sheet

1. NDA **203137**
2. REVIEW # 1
3. REVIEW DATE: 28-Jun-2013
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None.
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	26-Oct-2012
Amendment	31-Jan-2013
Amendment	11-Feb-2013
Amendment	20-May-2013

7. NAME & ADDRESS OF APPLICANT:

Name: GE Healthcare

Address: 1 Carnegie Center, Princeton NJ 08450, USA

Representative: Kevin Darryl White, MBA, RAC or
Paula Clark, Global Regulatory Lead

Telephone: KDW – (609) 514-6025
PC – (609) 514-6883

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vizamyl
- b) Non-Proprietary Name (USAN): Flutemetamol F 18
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

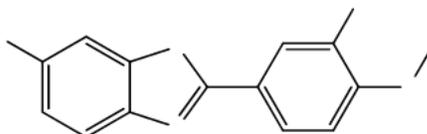
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging

11. DOSAGE FORM: Solution for Injection

Executive Summary Section

12. STRENGTH/POTENCY: 5 mCi (185 MBq)
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:

6-Benzothiazolol, 2-[3-[¹⁸F] fluoro-4-(methylamino) phenyl]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	(b) (4)	(b) (4)	4	N/A	N/A	
	II			7	N/A	N/A	The primary purpose is the sterilization process. Reviewed by microbiology.
	V			7	N/A	N/A	This is really a type I facility DMF, which the review division no longer reviews.

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Executive Summary Section

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
IND	101866	Applicant's Flutemetamol F 18 Injection IND.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Approval		
EES	Pending		
Pharm/Tox	Approval	27-Jun-2013	Sally Hargus, Ph.D.
Biopharm	Not Applicable		
LNC	N/A		
Methods Validation	PET product – Not submitted		
OSE/DMEPA	Proprietary name Vizamyl is acceptable	14-Feb-2013	Kevin Wright, PharmD
EA	Acceptable	Date of this review	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	18-Jun-2013	Robert J. Mello, Ph.D.

The Chemistry Review for NDA 203137

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided an acceptable from office of compliance for manufacturing facility inspections is received, and acceptable final package insert and container closure labeling is received.

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

The method for the determination of Flutemetamol is not sufficiently specific in that the flutemetamol peak is not resolved from the specified impurity (b)(4). Hence flutemetamol is quantified along with impurity (b)(4) and reported as such. Provide commitment that within 1 year of the date of approval of this New Drug Application you will submit method(s) that can specifically quantify flutemetamol and the (b)(4) impurity. You will also amend the finished product specifications to provide for acceptance criteria for flutemetamol amount and for (b)(4) impurity amount.

II. Summary of Chemistry Assessments

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

Vizamyl (Flutemetamol F 18 Injection) drug product is produced as a sterile solution for intravenous injection in a 10 ml or 30 ml multi-dose vial containing 150 mBq/mL (4.05 mCi/mL) of flutemetamol F 18 at reference date and time and up to 2 micrograms of flutemetamol. Each mL of the solution also contains 70 microliters of ethanol, 9.0 mg sodium chloride, 4.98 mg polysorbate 80 (w/v) in 0.014 M aqueous phosphate buffer. The pH of the solution is between 6.0 and 8.5. Based on the data, the proposed **shelf life of up to 10 hours is acceptable** for Flutemetamol F18 Injection, when manufactured at radioactive concentration of up to (b)(4). The drug product can be stored at 2°C to 30°C in the described container closure systems. Temperature excursions up to (b)(4) are tolerated.

The unit dose is prepared by the radio-pharmacy and is 185 MBq (5 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 ml, therefore a maximum of (b)(4) microliters of ethanol, (b)(4) mg sodium chloride (b)(4) mg polysorbate 80 (w/v) in 0.9% sodium chloride injection, USP may be present in the human dose. For smaller unit dose volumes (less than 10 mL), the ratios of polysorbate 80, ethanol and Sodium Chloride are maintained. The composition of the drug product is not altered (no dilution) after manufacture of the multi-dose vial of the drug product in preparation of the unit radio-pharmacy doses.

The Osmolality of Drug Product formulation was experimentally determined to be 1700 mOsm/kg. (b)(4)

However, since ethanol readily diffuses through the cell membrane, the ethanol does not contribute significantly to the physiological tonicity (osmotic pressure). *In vitro* evaluation of the potential for the formulation to induce haemolysis had shown no such effect and it was concluded that the formulation is compatible with intravenous injection to man

The drug substance, flutemetamol F 18, contains (b)(4)

Executive Summary Section

(b) (4)

Flutemetamol F 18 Injection typically contains less than 2 µg/mL flutemetamol.

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

Vizamyl (Flutemetamol F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations.

The recommended single intravenous dose for Vizamyl is 185 MBq (5 mCi) of flutemetamol F18 in a dose volume of ≤10 mL. The Vizamyl dose is administered by intravenous injection followed by 5 - 15 mL flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. Subsequent to administration (about 90 minutes later) the subject is imaged for 20 minutes using a PET camera.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an approval action, provided manufacturing facilities are found to be acceptable by Office of Compliance and the applicant submits acceptable labeling, for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance and the final intermediate.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are either adequate or there is sufficient information in the product application.
- The microbiology has recommended approval action from product quality microbiology (18-Jun-2013).
- There are no outstanding issues with specifications, methods and impurities.
- The stability of the product has been sufficiently demonstrated to support a 10 hour expiration dating period.

III. Administrative**A. Reviewer's Signature**

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Chemist Name: Ravindra K. Kasliwal, Ph.D.
CMC Lead Name: Eldon E. Leutzinger, Ph.D.
CMC Branch Chief (acting) Name: Danae Christadoulou, Ph.D.
Project Manager Name: Sharon Thomas (DMIP)

C. CC Block – See DARRTS

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/s/

RAVINDRA K KASLIWAL
06/28/2013

ELDON E LEUTZINGER
06/28/2013

DANAE D CHRISTODOULOU
06/28/2013
Concur with the reviewer's conclusions and recommendations

Initial Quality Assessment (IQA)
Branch VII

Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging Products (DMIP)

NDA: **203137**

Applicant: GE Healthcare, 101 Carnegie Center, Princeton NJ 08450, USA

Stamp Date: 26-Oct-2012

PDUFA Date: 26-Oct-2013

Trademark: VIZAMYL

Established Name: flutemetamol F 18

Laboratory Code: None

Dosage Form: Injection solution

Route of Administration: Intravenous Injection

Dose: 5 mCi (185 MBq)

Strength: 4.05 mCi/mL (150 MBq/ mL)

Indication: Flutemetamol F 18 Injection is a diagnostic radiopharmaceutical for intravenous injection. It has been developed for use with positron emission tomography (PET) imaging for the visual detection of fibrillar amyloid b, in the form of neuritic plaques, in the brain. The presence of neuritic plaques is one of two hallmarks of Alzheimer's disease (AD); the other is neurofibrillary tangles. The absence of brain amyloid rules out AD.

CMC Reviewer: Ravindra K. Kasliwal, Ph.D.

YES **NO**

ONDQA Fileability: X

Comments for 74-Day Letter X

Summary and Critical Issues:

A. Summary

Background Summary

The application is submitted as a 505(b) (1) new drug application (NDA) to obtain approval to market Flutemetamol F 18 Injection as a diagnostic radiopharmaceutical product for use with positron emission tomography (PET) imaging for the visual detection of fibrillar amyloid beta in the brain. It is intended for intravenous administration and is supplied as a sterile, phosphate buffered aqueous solution for multi-dose use containing 150 MBq/ml [¹⁸F] flutemetamol at reference time and date. [¹⁸F] fluorine disintegrates by positron emission with a half-life of 109.8 minutes, and the proposed shelf life for Flutemetamol F 18 Injection is 10 hours. The proposed commercial name for Flutemetamol F 18 Injection is VIZAMYL. The proposed Indications are:



(b) (4)

Drug Substance Summary:

The drug substance contained in Flutemetamol F18 Injection is [¹⁸F]flutemetamol (USAN). Chemically, it is 6-benzothiazolol, 2-[3-[¹⁸F] fluoro-4-(methylamino) phenyl]. The radioisotope fluorine-18 in flutemetamol F18 disintegrates by positron emission with a physical half-life of 109.8 minutes.



(b) (4)

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

NDA FILING CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		The NDA is e-CTD.
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Provided as attachment to FDA form 356H.

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	Is additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		The radioactive drug substance is manufactured in-situ during the manufacture of the drug product.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		The radioactive drug substance is manufactured in-situ during the manufacture of the drug product.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		The details are provided in pharmaceutical Development section 3.2.P.2.2.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		I

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		The micro section is part of the module 3 of the e-CTD.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMF for closure formulation is not provided. It is not clear if the DMF (b) (4) contains proprietary closure information.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	V	(b) (4)	(b) (4)	24-Aug-2011	Needs Review
	II			02-Aug-2011	Needs Review
	V			04-Feb-2012	Needs Review

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See the comments that should be forwarded to the applicant in 74-day letter of before.

{See appended electronic signature page}

Ravindra K. Kasliwal, Ph.D.
 CMC Reviewer
 Branch VII
 Division of New Drug Quality Assessment-III
 Office of New Drug Quality Assessment

16-Nov-2012

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
 Branch Chief
 Branch VII
 Division of New Drug Quality Assessment-III
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16-Nov-2012

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

/s/

RAVINDRA K KASLIWAL
11/16/2012

ALI H AL HAKIM
11/16/2012