

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204677Orig1s000

CHEMISTRY REVIEW(S)

NDA 204 677

**NeuraCeq
(Florbetaben F18) Injection**
50 to 5000 MBq/mL (1.35 to 135 mCi/mL)

Piramal Imaging, S.A.

**Chemistry, Manufacturing, and Controls
Division Director's Summary Basis of Action**

Applicant: Piramal Imaging S.A.
c/o Pascale Nguyen
1753 Matran, Switzerland

Indication:

NeuraCeq™ 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) and other causes of cognitive decline. A negative NeuraCeq 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 NeuraCeq scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid 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. NeuraCeq is an adjunct to other diagnostic evaluations. (1).

Presentation:

NeuraCeq is available in 30 mL multi-dose vials containing a clear solution at a strength of 50-5000 MBq/mL (1.4-135 mCi/mL) florbetaben F18 at EOS.

EER Status: Recommendation: **All acceptable as of December 12, 2013.**

Consults

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending	22-Aug-2013	
Pharm/Tox	Acceptable	22-Aug-2013	Sunday O. Awe, Ph.D.
Biopharm	Not Applicable		
Labeling Nomenclature Committee (LNC)	Not Applicable		
Methods Validation	Not Requested		
DMEPA/OSE	Proprietary name is acceptable	16-Jul-2013	Kevin Wright, PharmD
EA	Categorically excluded from the requirement to prepare an Environmental Assessment.	22-Aug-2013	Anne Marie Russell, Ph.D.
Microbiology	Approval	12-Aug-2013	Erika Pfeiler, Ph.D.

DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	(b) (4)	(b) (4)	3, 4	Adequate	13-Aug-2013	Microbiology review
	V			1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.
	V			1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.
	V			1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.

Synthesis Module DMFs

Description	DMF number	Date DMF Submitted to FDA	DMF Holder	Letter of Cross Reference
	(b) (4)	23 Aug 2011	(b) (4)	Module 1.4.4
		31 Aug 2011		Module 1.4.4
		29 Aug 2011		Module 1.4.4

Background:

Florbetaben F 18 Injection is produced as a sterile solution for intravenous injection in a 30 mL multi-dose vial containing 50 mBq/mL (1.35 mCi/mL) to 5000 mBq/mL (135 mCi/mL) of Florbetaben F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.4 mg of ascorbic acid, USP, 118 mg ethanol (b) (4), USP, 200 mg Macrogol 400, USP, 28.8 mg of sodium ascorbate, USP, and 677.5 mg (b) (4) water for injections. Florbetaben F 18 Injection contains NMT 3 µg/mL florbetaben.

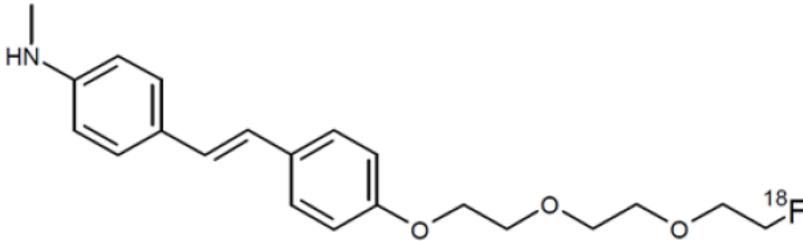
The unit dose is prepared by the radio-pharmacy and is 300 MBq (81 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 mL, therefore a maximum of 44 mg of ascorbic acid, USP, 1.18 g ethanol (b) (4) USP, 2.00 mg Macrogol 400, USP, 0.288 g of sodium ascorbate, USP, and 6.775 g (b) (4) water for injections may be present in the human dose. (b) (4)

The Drug Substance, florbetaben F 18, contains the radioactive isotope fluorine-18 (F-18). F-18 undergoes radioactive decay primarily (96.9% abundance) through emission of a positively charged beta particle (positron; β+) having maximum and average energies of 634 and 249 keV, respectively. The half-life of F-18 is 109.77 minutes. A positron generated from F-18 decay travels a maximum distance of 2.4 mm (mean linear range = 0.2 mm) in tissue until it collides with an electron and annihilates. The annihilation event produces two 511 keV gamma photons which are emitted 180° to one another. It is the coincidental detection of these two 511 keV gamma photons which forms the basis for positron emission tomographic imaging. F-18 decays to stable O-18 oxygen.

The Drug Substance (florbetaben F 18) in Florbetaben F 18 Injection is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity (MBq/µg) at the end of synthesis (EOS) is required to be not less than (NLT) (b) (4). The specific activity is required to be NLT (b) (4) at expiry. The strength (concentration) of Drug Substance in Drug Product is required to be NLT 50 MBq/mL and NMT 5000 MBq/mL at EOS and is required to be NLT (b) (4) at expiry. The shelf-life (expiry) specifications mean that a 300 MBq maximum human dose of Florbetaben F 18 Injection will contain not more than (b) (4) and will be

contained in not more than 10 mL of a solution.

Drug Substance:



The drug substance is (b) (4) in the manufacture of Flurbiprofen. The drug substance and drug product are manufactured (b) (4) Flurbiprofen API is produced from a (b) (4) manufactured by (b) (4):

(b) (4)

Following several exchanges of information requests and responses the impurities specifications for the (b) (4) were agreed upon. All (b) (4) specifications are acceptable. Note that the (b) (4) has a stability retest of (b) (4).

Drug Substance: Satisfactory

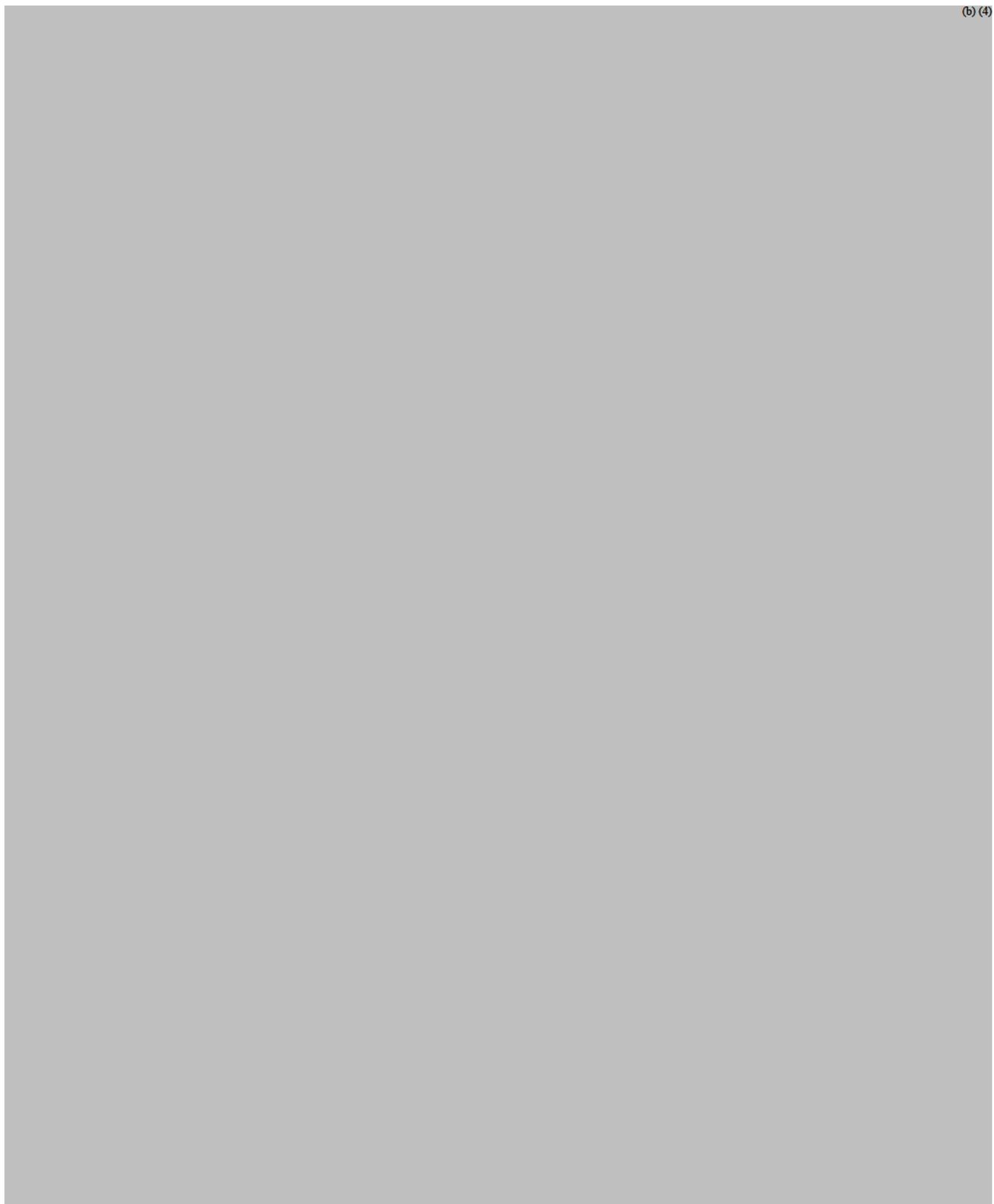
Drug Product:

The drug product contains the following excipients: ascorbic acid, (b) (4) ethanol, Macrogel 400 (polyethylene glycol), sodium ascorbate and (b) (4) water for injection. All are USP. (b) (4)

(b) (4)

Florbetaben solution for injection is produced according to the following flow chart

(b) (4)



Drug Product: Satisfactory.

Labeling:

Pig, container labels and package insert are acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

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/s/

ERIC P DUFFY
03/18/2014

NDA 204 677

**Neuraceq
(Florbetaben F18) Injection
Piramal Imaging, S.A.**

**Anne Marie Russell, Ph.D.
Review Chemist**

**Office of New Drug Quality Assessment
Division I Branch II
for
The Division of Medical Imaging Products**

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Chemistry Review Data Sheet

1. NDA 204-677
2. REVIEW #3 (follow-up memo for Review #2 dated 13-Dec-2013)
3. REVIEW DATE: 5-Feb-2013
4. REVIEWERS: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS: Reviewed in CMC Reviews #1 and #2

Submission type	Content	Date Letter date in EDR	EDR Sequence Number
Original	NDA	21-DEC-2012	1
Amendment	Response to comments in 74 Day letter	26-April-2013	11
Amendment	Response to CMC IR#1	31-May-2013	15
Amendment	Response to CMC IR#2	18-Sept-2013	23
Amendment	Response to CMC IR#3	18-Sept-2013	24
Amendment	Response to CMC IR#4	Submitted by email 18-Nov-2013	
Amendment	Revised Response to CMC IR#4 (after tcon)	04-Dec-2013	36
Amendment	Withdraw (b) (4) manufacturing site	11-Dec-2013	38

6. SUBMISSION(S) BEING REVIEWED:

Submission type	Content	Date Letter date in EDR	Supporting Document Number
Amendment	Revised carton and container labeling	25-Sept-2013	28
Amendment	Response to CMC IR#4 (official submission of response sent previously on 18-Nov-2013 by email)	13-Dec-2013	39
Amendment	Unsolicited revisions to CMC portions of the NDA (see review)	14-Jan-2014	40
Amendment	Revised Package Insert labeling – response to DDMAC comments	16-Jan-2014	41
By email	Responses to CMC comments on labeling		

7. NAME & ADDRESS OF APPLICANT:

Name: Piramal Imaging SA
Address: Route de l'Ecole 13
c/o Pascale Nguyen
1753 Matran, Switzerland

Authorized Jeanne M. Novak, Ph.D., CBR International Corp.
U.S. Agent: 2905 Wilderness Place, Suite 202 Boulder, CO 80301

Telephone: 720-746-1190

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: none
- b) Non-Proprietary Name (USAN): florbetaben
- c) Code Name/# (ONDQA only): BAY94-9172
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem Type: 1 (new molecular entity)
 - Submission Priority: standard

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

NDA 204-677 was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: positron emission tomography (PET) tracer

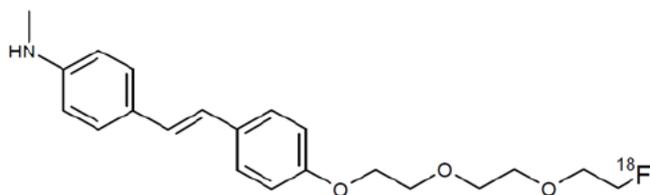
11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: per form 356: 300 MBq per dose, 50 – 5000 MBq (1.35 – 135 mCi) per mL at calibration time
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:

4-[(E)-2-(4-{2-[2-(2 [18F]fluoroethoxy)ethoxy]ethoxy}phenyl)vinyl]-N-methylaniline

1. Structural Formula



2. Molecular Formula

$C_{21}H_{26}^{18}F NO_3$

3. Relative Molecular Weight

358.45

17. RELATED/SUPPORTING DOCUMENTS: see CMC Review #1 and #2
18. STATUS: see CMC Review#1 and #2

The Chemistry Review for NDA 204-677

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.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

See CMC Review #1 and #2

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

See CMC Review #1 and #2

C. Basis for Approvability or Not-Approval Recommendation

See CMC Review #1 and #2.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*

Primary review: Anne Marie Russell, Ph.D., CMC reviewer

B. Endorsement Block *{see electronic signature page}*

Eldon Leutzinger, Ph.D., CMC Lead, Branch VII

Danae Christodoulou, Ph.D., Branch Chief, Acting , Branch VII

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/s/

ANNE M RUSSELL
03/07/2014

ELDON E LEUTZINGER
03/07/2014

DANAE D CHRISTODOULOU
03/10/2014

NDA 204 677

**Neuraceq
(Florbetaben F18) Injection
Piramal Imaging, S.A.**

**Anne Marie Russell, Ph.D.
Review Chemist**

**Office of New Drug Quality Assessment
Division I Branch II
for
The Division of Medical Imaging Products**

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Chemistry Review Data Sheet

1. NDA 204-677
2. REVIEW #2 (follow-up memo for Review #1)
3. REVIEW DATE: 12-Dec-2013
4. REVIEWERS: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS: Reviewed in CMC Review #1 (August 2013)

Submission type	Content	Date Letter date in EDR	EDR Sequence Number
Original	NDA	21-DEC-2012	1
Amendment	Response to comments in 74 Day letter	26-April-2013	11
Amendment	Response to IR#1	31-May-2013	15

6. SUBMISSION(S) BEING REVIEWED:

Submission type	Content	Date Letter date in EDR	Supporting Document Number
Amendment	Response to IR#2	18-Sept-2013	23
Amendment	Response to IR#3	18-Sept-2013	24
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7. NAME & ADDRESS OF APPLICANT:

Name: Piramal Imaging SA
Address: Route de l'Ecole 13
c/o Pascale Nguyen
1753 Matran, Switzerland

Authorized: Jeanne M. Novak, Ph.D., CBR International Corp.
U.S. Agent: 2905 Wilderness Place, Suite 202 Boulder, CO 80301

Telephone: 720-746-1190

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: none
- b) Non-Proprietary Name (USAN): florbetaben
- c) Code Name/# (ONDQA only): BAY94-9172
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem Type: 1 (new molecular entity)
 - Submission Priority: standard

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

NDA 204-677 was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: positron emission tomography (PET) tracer

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: per form 356: 300 MBq per dose, 50 – 5000 MBq (1.35 – 135 mCi) per mL at calibration time

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

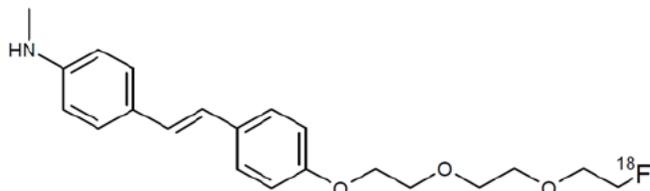
SPOTS product – Form Completed

Not a SPOTS product

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

4-[(E)-2-(4-{2-[2-(2 [¹⁸F]fluoroethoxy)ethoxy]ethoxy}phenyl)vinyl]-N-methylaniline

1. Structural Formula



2. Molecular Formula

$C_{21}H_{26}^{18}F NO_3$

3. Relative Molecular Weight

358.45

17. RELATED/SUPPORTING DOCUMENTS: see CMC Review #1

18. STATUS: see CMC Review#1

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12-Dec-2013	Office of Compliance

The Chemistry Review for NDA 204-677

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 there is an acceptable final package insert and container closure labeling.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

See CMC Review #1

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

See CMC Review #1

C. Basis for Approvability or Not-Approval Recommendation

See CMC Review #1.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*

Primary review: Anne Marie Russell, Ph.D., CMC reviewer

B. Endorsement Block *{see electronic signature page}*

Eldon Leutzinger, Ph.D., CMC Lead, Branch VII

Danae Christodoulou, Ph.D., Branch Chief, Acting , Branch VII

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/s/

ANNE M RUSSELL
12/13/2013

ELDON E LEUTZINGER
12/13/2013

DANAE D CHRISTODOULOU
12/13/2013

I concur with the reviewer's conclusion and recommendations
Edit on Cover Page: This review was done in ONDQA Div. III, Branch VII

NDA 204 677

**Neuraceq
(Florbetaben F18) Injection
Piramal Imaging, S.A.**

**Anne Marie Russell, Ph.D.
Review Chemist**

**Office of New Drug Quality Assessment
Division I Branch II
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The Division of Medical Imaging Products**

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 B. Environmental Assessment Or Claim Of Categorical Exclusion Evaluation: 97

Chemistry Review Data Sheet

1. NDA 204-677
2. REVIEW #1
3. REVIEW DATE: 22-August-2013
4. REVIEWERS: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS: None (IND 78,868 Bayer HealthCare Pharmaceuticals, Inc.)
6. SUBMISSION(S) BEING REVIEWED:

Submission type	Content	Date Letter date in EDR	EDR Sequence Number
Original	NDA	21-DEC-2012	1
Amendment	Response to comments in 74 Day letter	26-April-2013	11
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- c) Code Name/# (ONDQA only): BAY94-9172
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem Type: 1 (new molecular entity)
 - Submission Priority: standard

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

NDA 204-677 was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: positron emission tomography (PET) tracer

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: per form 356: 300 MBq per dose, 50 – 5000 MBq (1.35 – 135 mCi) per mL at calibration time

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

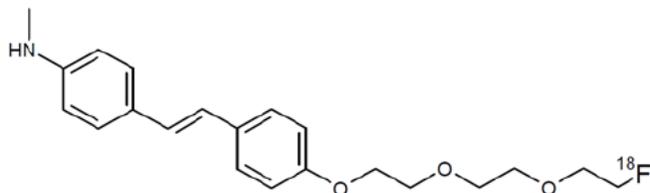
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1. Structural Formula



2. Molecular Formula

$C_{21}H_{26}^{18}F NO_3$

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V	(b) (4)	(b) (4)	3, 4	Adequate	13-Aug-2013	Microbiology review
(b) (4)	V	(b) (4)	(b) (4)	1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.
(b) (4)	V	(b) (4)	(b) (4)	1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.
(b) (4)	V	(b) (4)	(b) (4)	1	Adequate	22-Aug-2013	CMC review of DMF by Anne Marie Russell, Ph.D.

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: IND 78,868

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending	22-Aug-2013	
Pharm/Tox	Acceptable	22-Aug-2013	Sunday O. Awe, Ph.D.
Biopharm	Not Applicable		
Labeling Nomenclature Committee (LNC)	Not Applicable		
Methods Validation	Not Requested		
DMEPA/OSE	Proprietary name is acceptable	16-Jul-2013	Kevin Wright, PharmD
EA	Categorically excluded from the requirement to prepare an Environmental Assessment.	22-Aug-2013	Anne Marie Russell, Ph.D.
Microbiology	Approval	12-Aug-2013	Erika Pfeiler, Ph.D.

The Chemistry Review for NDA 204-677

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

- i. The manufacturing facility inspections are found acceptable from the Office of C
- ii. There is an acceptable final package insert and container closure labeling
- iii. All outstanding CMC issues are resolved.

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 Substance and Drug Product

Florbetaben F 18 Injection is produced as a sterile solution for intravenous injection in a 30 mL multi-dose vial containing 50 mBq/mL (1.35 mCi/mL) to 5000 mBq/mL (135 mCi/mL) of Florbetaben F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.4 mg of ascorbic acid, USP, 118 mg ethanol (b)(4) USP, 200 mg Macrogol 400, USP, 28.8 mg of sodium ascorbate, USP, and 677.5 mg (b)(4) water for injections. Florbetaben F 18 Injection contains NMT 3 µg/mL florbetaben.

The unit dose is prepared by the radio-pharmacy and is 300 MBq (81 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 44 mg of ascorbic acid, USP, 1.18 g ethanol (b)(4) USP, 2.00 mg Macrogol 400, USP, 0.288 g of sodium ascorbate, USP, and 6.775 g (b)(4) water for injections may be present in the human dose. (b)(4)

The Drug Substance, florbetaben F 18, contains the radioactive isotope fluorine-18 (F-18). F-18 undergoes radioactive decay primarily (96.9% abundance) through emission of a positively charged beta particle (positron; β^+) having maximum and average energies of 634 and 249 keV, respectively. The half-life of F-18 is 109.77 minutes. A positron generated from F-18 decay travels a maximum distance of 2.4 mm (mean linear range = 0.2 mm) in tissue until it collides with an electron and annihilates. The annihilation event produces two 511 keV gamma photons which are emitted 180° to one another. It is the coincidental detection of these two 511 keV gamma photons which forms the basis for positron emission tomographic imaging. F-18 decays to stable O-18 oxygen.

The Drug Substance (florbetaben F 18) in Florbetaben F 18 Injection is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity (MBq/ μ g) at the end of synthesis (EOS) is required to be not less than (NLT) (b) (4). The specific activity is required to be NLT (b) (4) MBq/mol at expiry. The strength (concentration) of Drug Substance in Drug Product is required to be NLT 50 MBq/mL and NMT 5000 MBq/mL at EOS and is required to be NLT (b) (4) at expiry. The shelf-life (expiry) specifications mean that a 300 MBq maximum human dose of Florbetaben F 18 Injection will contain not more than (b) (4) and will be contained in not more than 10 mL of a solution.

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

Neuraceq (Florbetaben F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid in the brain.

The recommended single intravenous dose for Neuraceq is 300 MBq (81 mCi) of florbetaben F18 in a dose volume of \leq 10 mL. The Neuraceq dose is administered as a slow intravenous injection push.

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 and responses that address our comments) 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.
- 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 microbiology has recommended approval action from product quality microbiology.
- The stability of the product has been sufficiently demonstrated to support a 10 hour expiration dating period.
- The referenced drug master files (DMF) are adequate to support the product application.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*

Primary review: Anne Marie Russell, Ph.D., CMC reviewer

B. Endorsement Block *{see electronic signature page}*

Eldon Leutzinger, Ph.D., CMC Lead, Branch VII

Danae Christodoulou, Ph.D., Branch Chief, Acting, Branch VII

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/s/

ANNE M RUSSELL
08/23/2013

ELDON E LEUTZINGER
08/23/2013

DANAE D CHRISTODOULOU
08/23/2013

I concur with the reviewer's conclusions and recommendations

Initial Quality Assessment (IQA)
For
Division of New Drug Quality Assessment III, Branch VII
Office of New Drug Quality Assessment

OND Division: DMIP
NDA: 204-677
Applicant: Piramal Life Sciences
Route de l'Ecole 13
c/o Pascale Nguyen
1753 Matran, Switzerland
Stamp Date: 12/21/2012
PDUFA: 12/21/2013
Trademark: TBD
Established: Florbetaben for Injection
Dosage Form: Sterile solution
Route of Administration: IV
Strength: 50 – 5000 MBq (1.35 – 135 mCi) per mL

Indication: for detection of beta-amyloid in the brain, thereby resulting in the differential diagnosis in adult patients who are evaluated for Alzheimer' disease and other causes of cognitive decline

Chemical Type: NME (**Type 1**)

CMC Lead: Eldon E. Leutzinger, Ph.D., Branch VII

ONDQA Fileability YES NO
Will leave this be a joint decision by the CMC review team, but tentatively yes.

Comments for 74-Day Letter (there will be comments for the filing letter)
If filed, will leave this to the primary reviewer, but have provided a preliminary assessment.

Summary and Critical Issues:

A. Summary

The **Drug Product** is an aqueous solution of [¹⁸F]Florbetaben, with excipients, packaged in a 30 mL colorless glass vial (Type 1), (b)(4) gray stopper and sealed with aluminum seal. It is difficult to find a defined volume of the product in the 30 ml vial. There is a dose indicated in the Form 356h (300 MBq per dose; or 8 mCi per dose). In 3.2.P.1.02-01 (explanation they give under the formulation table on next review page), they say that at the time of administration, 300 MBq (8 mCi) are contained in (b)(4) 10 mL of drug product. But, this does not say that there is maximally 10 mL volume in the 30 mL vial. It could be less, or it could be more, as it often times works out with

radiopharmaceuticals. I have not been able to find a volume in the batch records, nor a volume in the release specifications. My educated guess is that it would be 10 mL. Because this appears to be so nebulous, the primary reviewer needs to search the NDA for maximal volume in the 30 mL more closely than expected for an initial review, and this may need to be requested of Piramal (**Critical Issue #1**).

Formulation:

Each mL of drug product contains the following ingredients (reproduced from 3.2.P.1.02-01. See the next review page.

(Formulation contd):

Each 1 mL Florbetaben solution for injection contains:

Composition	Reference to standard	Function	Weight [mg]	Volume [mL]
Total drug substance				
¹⁸ F-Florbetaben (b) (4)	specification	(b) (4)	≤ 0.003	
Excipients				
Ascorbic acid	Ph. Eur, USP, Ph. Jap.		4.4	
Ethanol (b) (4)	Ph. Eur, USP, Ph. Jap.		118	
Macrogol 400	Ph. Eur, NF, Ph. Jap.		200	
(syn. Polyethylene glycol 400)				
Sodium ascorbate	Ph. Eur, USP, JPE		28.8	
(b) (4) water for injections	Ph. Eur, USP, Ph. Jap.		677.5	
Filling amount			1028.7	1.0 ^a
a (b) (4)				

Each batch of final drug product at release will contain 50 – 5000 MBq/mL (1.35 – 135 mCi/mL) of ¹⁸F-radioactivity and ≤ 3 µg/mL of Florbetaben (b) (4)

(b) (4) see my explanation on the next review page (Florbetaben Manufacturing Principle, #1). It is not possible to exclude (b) (4) from the process. (b) (4)

(b) (4)

(b) (4)

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B. NDA Filing Checklist

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		
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		Per CMC issues; but information not complete for mfg sites (e.g., absence of FEI numbers). Full addresses of sites are provided, and listed as ready for inspection.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i> .				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Section 3.2.S.2.1-01-01 Section 3.2.P.3.1-01-01
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

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <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		Did not see any FEI numbers, so may not be previously registered with FDA; also, there is no contact information provided for each mfg site (but, there is a US Agent listed in the 356h form)
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <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		Did not see any FEI numbers; same as above

	Parameter	Yes	No	Comment
9.	<p>Are 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:</p> <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) 			Not Applicable
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Cover letter

C. ENVIRONMENTAL ASSESMENT

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

D. MASTER FILES (DMF/MAF)

	Parameter	Yes	No	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See next page

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	V	(b) (4)	(b) (4)	August 5, 2011	Note that this is a biologics DMF

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
13.	Does the section contain a description of the DS manufacturing process?	X		See drug product, since drug substance is <i>in situ</i> ; the controls for (b) (4) should rise to the same level as a drug substance (see IQA)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	X		(b) (4)
15.	Does the section contain information on impurities?	X		See Drug Product
16.	Does the section contain information regarding the characterization of the DS?	X		
17.	Does the section contain controls for the DS?	X		
18.	Has stability data and analysis been provided for the drug substance?			N/A; drug substance is produced (b) (4) – see drug product
19.	Does the application contain Quality by Design (QbD) information regarding the DS?			N/A
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			N/A
21.	Does the section contain container and closure information?	X		

F. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
22.	Does the section contain quality controls of excipients?	X		
23.	Does the section contain information on composition?	X		
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
25.	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		
26.	Is there a batch production record and a proposed master batch record?	X		
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
28.	Have any biowaivers been requested?			N/A
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
30.	Does the section contain controls of the final drug product?	X		
31.	Has stability data and analysis been provided to support the requested expiration date?	X		
32.	Does the application contain Quality by Design (QbD) information regarding the DP?			N/A
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			N/A

G. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
34.	Is there a methods validation package?	X		

H. MICROBIOLOGY					
	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	X			See Microbiology reviews

I. LABELING				
	Parameter	Yes	No	Comment
36.	Has the draft package insert been provided?	X		
37.	Have the immediate container and carton labels been provided?	X		
38.	Does section contain tradename and established name?	X		

J. FILING CONCLUSIONS				
	Parameter	Yes	No	Comment
39.	Is the product quality section of the application fileable?	X		But, will need additional information on mfg sites (e.g., there are no FEI numbers listed, so we don't know at this point whether any of the sites are registered with the FDA; also, there are no contacts for each of the sites – only the US Agent listed in the 356h form.
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the applicant			N/A
41.	Are there any potential review issues to be forwarded to the applicant for the 74 day letter?			May be decided joint with primary reviewer

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{See appended electronic signature page}

NAME: Eldon E. Leutzinger, Ph.D.

CMC-Lead

Division of Pre-Marketing Assessment III, Branch VII

Office of New Drug Quality Assessment

{See appended electronic signature page}

NAME: Danae D. Christodoulou, Ph.D.

Branch Chief

Division of Pre-Marketing Assessment III, Branch VII

Office of New Drug Quality Assessmentg

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/s/

ELDON E LEUTZINGER
02/12/2013

DANAE D CHRISTODOULOU
02/12/2013

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

Application: NDA 204677/000
Code: 160
Priority: 1
Stamp Date: 21-DEC-2012
PDUFA Date: 21-MAR-2014
Action Goal:
District Goal: 20-JAN-2014

Sponsor: PIRAMAL IMAGING
 2905 WILDERNESS PL STE 202
 BOULDER, CO 80301
Brand Name: (INN): FLORBETABEN
Estab. Name:
Generic Name: (INN): FLORBETABEN
Product Number; Dosage Form; Ingredient; Strengths
 001; SOLUTION, INJECTION; FLORBETABEN F-18; 1.35-135mCi

FDA Contacts:	A. RUSSELL	Prod Qual Reviewer	(HFD-530)	3017962014
	Y. LIU	Product Quality PM		3017961926
	S. THOMAS	Regulatory Project Mgr		3017961994
	E. LEUTZINGER	Team Leader		3017961399

Overall Recommendation:	ACCEPTABLE	on 12-DEC-2013	by R. WITTORF	()	2404023113
	WITHHOLD	on 25-NOV-2013	by R. WITTORF	()	2404023113
	PENDING	on 05-FEB-2013	by EES_PROD		
	PENDING	on 05-FEB-2013	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMR No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER

Profile: [REDACTED] (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-FEB-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Establishment: **CFN:** **FEI:** [REDACTED] (b) (4)
IBA MOLECULAR NORTH AMERICA INC

DMF No: [REDACTED] (b) (4) **ADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-FEB-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** [REDACTED] (b) (4)
IBA MOLECULAR NORTH AMERICA, INC.

DMF No: [REDACTED] (b) (4) **ADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION
