CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204677Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	February 12, 2014
Reviewer(s):	Amarilys Vega, MD, MPH, Medical Officer, Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, PharmD, Team Leader, DRISK
Division Director	Claudia Manzo, Pharm.D, Director
	DRISK
Subject:	Review Addendum
Drug Name(s):	Florbetaben F-18 for Injection
Therapeutic Class:	Radiopharmaceutical (diagnostic imaging agent for Positron Emission Tomography (PET))
Dosage and Route:	300 MBq (8.1 mCi)/single intravenous bolus
Application Type/Number:	NDA 204677
Applicant/sponsor:	Piramal Imaging S.A.
OSE RCM #:	2013-21

*** This document contains proprietary and confidential information that should not be released to the public. ***

1. INTRODUCTION

This review is an addendum to DRISK's review dated August 30, 2013, in which DRISK deferred comments on the need for a Risk Evaluation and Mitigation Strategy (REMS) for florbetaben F-18 injection (NeuraCeq™, NDA 204677, initially submitted on December 21, 2012). Piramal Imaging is seeking approval for florbetaben for the detection of β-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline.

On November 22, 2013, Piramal submitted to FDA an additional clinical study: "A non-interventional study to assess the efficacy, reliability, and reproducibility of the florbetaben-F18 (FBB) β-amyloid Positron Emission Tomography (PET) scan visual assessment method as trained via an electronic training tool, using images from the histopathology study 14595". This submission was considered a major amendment, extending the PDUFA review goal date from December 21, 2013 to March 21, 2014.

Piramal Imaging did not submit a REMS or risk management plan with their December 21, 2012 or November 22, 2013 submissions.

1.1. Materials Reviewed

Following is a list of the materials reviewed.

- NDA submission from November 22, 2013
- Brenda Ye, M.D., Clinical Review, dated August 23, 2013 and January 31, 2014
- Lan Huang, Ph.D., Statistical Review, dated August 23, 2013 and January 31, 2014

1.2. Regulatory History

The regulatory history, in pertinent part, is as follows:

- **October 23, 2008:** Advisory committee meeting to obtain advice on the clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's disease. Post-mortem histopathology was proposed as an appropriate standard of truth (SoT) for efficacy.
- **December 21, 2012:** FDA receives NDA submission for florbetaben.
- **May 21, 2013:** Mid-cycle Communication to the Applicant addressed clinical concerns (imaging performance characteristics, particularly specificity) and microbiology and chemistry information requests.
- **October 29, 2013:** Wrap-up meeting. The Division of Medical Imaging Products (DMIP) concluded that the data in the original NDA are insufficient for assessing the effectiveness of florbetaben as an amyloid imaging agent.
- **November 22, 2013:** Piramal submited to FDA additional clinical data. This submission was considered a major amendment, which extended the PDUFA review goal date from December 21, 2013 to March 21, 2014.
- **January 16, 2014:** New mid-cycle meeting (due to a major amendment of this application). Statistical and clinical reviewers support approval of this application

with some reservations regarding efficacy results associated to low specificity for two of the readers.

- **March 21, 2014:** PDUFA date.

2. KEY REVIEW FINDINGS

The clinical and statistical reviewers determined that the data included in the November 22, 2013 submission provide adequate evidence of effectiveness of florbetaben for imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. Residual concerns regarding the efficacy data (i.e., low specificity of two of the readers) will be further evaluated by DMIP.

Similar to other radiopharmaceuticals, the main safety concern associated to the use of florbetaben is the risk of radiation exposure. Florbetaben contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer.

3. CONCLUSION AND RECOMMENDATIONS

The clinical development program demonstrated that florbetaben is effective and safe for the proposed indication. Florbetaben's safety profile is similar to that of other radiopharmaceuticals. No additional serious safety concerns were identified during the review.
DRISK concludes that a REMS is not necessary to manage the risk of radiation exposure associated to the use of florbetaben and concurs with DMIP's recommendation to manage this risk through labeling.

Please contact DRISK if you have any questions.

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/s/

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02/12/2014

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02/13/2014
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	August 30, 2013
Reviewer(s):	Amarilys Vega, MD, MPH, Medical Officer, Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, PharmD, Team Leader, DRISK
Subject:	Risk management assessment deferral
Drug Name(s):	Florbetaben F-18 for Injection
Therapeutic Class:	Radiopharmaceutical (diagnostic imaging agent for Positron Emission Tomography (PET))
Dosage and Route:	300 MBq (8.1 mCi)/single intravenous bolus
Application Type/Number:	NDA 204677
Applicant/sponsor:	Piramal Imaging S.A.
OSE RCM #:	2013-21

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1. INTRODUCTION

This review documents DRISK's defer to comment on if a Risk Evaluation and Mitigation Strategy (REMS) is necessary for florbetaben F-18 (florbetaben, NDA 204677, submitted on December 21, 2012). Piramal Imaging is seeking approval for florbetaben for the detection of β-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline.

Piramal Imaging did not submit a REMS or risk management plan with their December 21, 2012 submission.

Florbetaben is available in 30 mL vials containing a clear solution. A volume of up to 10 mL of florbetaben can be administered to provide at least 300 MBq (8.1 mCi) at the time of administration.

As of the time when this review was completed, florbetaben has not been approved in any other country.

1.1. Background

AD may develop at any time during adulthood and it is the most common cause of dementia in the elderly. The disease starts with memory loss and is followed by progressive dementia.[1] A definite diagnosis of AD requires post-mortem histopathological examination of the brain, which is characterized by the presence of extracellular deposits of β-amyloid peptides, intra-neuronal neurofibrillary tangles, and the predominance of neocortical neuronal degeneration.[2]

Florbetaben is labeled with a radioactive isotope [18F], which has a half-life of 110 minutes and is used for diagnostic purpose only, as a tracer in positron emission tomography (PET) imaging.[2] The development program for florbetaben assessed its ability to reliably detect β-amyloid in the brain, and to develop a standardized visual assessment method that can be used by different PET readers, with different cameras.

Amyvid (Florbetapir F 18 Injection) for intravenous use, a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain, was approved by FDA in 2012 to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

1.2. Materials Reviewed

Following is a list of the materials reviewed.

- NDA submission from December 21, 2012
  - Clinical Overview
  - Summary of Clinical Efficacy

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[1] Seeley W.W., Miller B.L. (2012). Chapter 371. Dementia. In D.L. Longo, A.S. Fauci, D.L. Kasper, S.L. Hauser, J.L. Jameson, J. Loscalzo (Eds), *Harrison's Principles of Internal Medicine*, 18e. Retrieved August 12, 2013 from http://www.accessmedicine.com/content.aspx?aID=9146233.

[2] Florbetaben F-18, Clinical Overview.

    - Summary of Clinical Safety
- Brenda Ye, M.D., Clinical Review, dated August 23, 2013.
- Lan Huang, Ph.D., Statistical Review, dated August 23, 2013.

1.3. Regulatory History

The regulatory history, in pertinent part, is as follows:

- **October 23, 2008:** Advisory committee meeting to obtain advice on the clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's disease. Post-mortem histopathology was proposed as an appropriate standard of truth (SoT) for efficacy.
- **December 21, 2012:** FDA receives NDA submission for florbetaben.
- **May 21, 2013:** Mid-cycle Communication Meeting with the Applicant.

Important upcoming dates:

- **October 29, 2013:** Wrap-up meeting.
- **December 21, 2013:** PDUFA date.

2. CLINICAL DEVELOPMENT PROGRAM

The clinical development program of florbetaben evaluated its efficacy through 9 clinical studies (6 Phase 1, 2 Phase 2, and 1 Phase 3) plus an additional pooled read study (Study 16034) including 461 images across most of these studies (plus a 10% re-read of randomly assigned 46 images). The pivotal Phase 3 study (Study 14595) evaluated the sensitivity and specificity of florbetaben when comparing PET images with histopathologic brain findings.[3] The pooled read study evaluated the reliability and reproducibility in a clinically applicable setting.

The safety profile of florbetaben is based on 990 administrations in 884 subjects; 978 administrations with florbetaben and 12 (in 12 subjects) with vehicle.[2]

3. KEY REVIEW FINDINGS

The clinical and statistical reviewers determined that the data included in the dossier does not provide adequate evidence of effectiveness (specificity in particular) and recommend the application receive a Complete Response letter. [4]

4. CONCLUSION AND RECOMMENDATIONS

At the time of this review the efficacy and safety of florbetaben for injection for used in PET scans for the detection of β-amyloid in the brain in patients undergoing evaluation for AD and other causes of cognitive decline have not been determined.

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[3] The design of Study 14595 required study participants' consent to donate their brain after death. These study subjects were end-of-life and/or terminally individuals – a population that is unlikely to represent the anticipated population of users once the drug is approved.

[4] Brenda Ye, M.D., Clinical Review, dated August 23, 2013; Lan Huang, Ph.D., Statistical Review, dated August 23, 2013.

Until the efficacy and safety profile of florbetaben is established, the benefits and risks of florbetaben cannot be adequately weighed and an appropriate risk management strategy cannot be determined. The Division of Medical Imaging Products plans to issue a Complete Response letter. Therefore, DRISK defers comment on the management of the risks associated with florbetaben and labeling at this time.

A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter.

Please contact DRISK if you have any questions.

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08/30/2013

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