

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203137Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Date:	June 21, 2013
Reviewer(s)	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader	Cynthia LaCivita, Pharm.D., Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm.D., Director, DRISK
Drug Name(s):	Vizamyl (flutemetamol F 18 injection)
Therapeutic class:	Diagnostic Molecular Imaging Agent
OND Review Division	Division of Medical Imaging Products
Application Type/Number:	NDA 203137
Application received	October 26, 2012
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Applicant/sponsor:	GE Healthcare
OSE RCM #:	2013-513
TSI #:	n/a

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1 INTRODUCTION

This document reviews the need for a risk evaluation and mitigation strategy (REMS) for Vizamyl (flutemetamol F 18 injection).

On October 26, 2012, GE Healthcare submitted a new drug application (NDA 203137) for Vizamyl. Vizamyl is a radioactive diagnostic agent with a proposed indication of Positron Emission Tomography (PET) imaging of the brain to estimate beta-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.

2 MATERIALS REVIEWED

We reviewed the following:

- Draft Vizamyl labeling, submitted by the applicant, as edited by the FDA through June 6, 2013
- Approved labeling for Amyvid (Florbetapir F 18 Injection), Lilly USA, 2012
- Approval letter for Amyvid (Florbetapir F 18 Injection), signed April 6, 2012
- Complete Response letter for Amyvid (Florbetapir F 18 Injection), signed March 17, 2011
- Minutes dated April 24, 2013 of a Mid-cycle Communication teleconference for NDA 203137 held between FDA and GE Healthcare on April 2, 2013
- Email communication dated May 20, 2013 from Dr. Dwaine Rieves to the clinical review team summarizing sensitivity and specificity of test results by trained readers for florbetapir (NDA 202008, approved agent for PET imaging of the brain to estimate beta-amyloid neuritic plaque density), flutemetamol (NDA 203137, the subject of this review), (b) (4)

- November 2012 review by Michael E. Kieffer, Pharm.D., M.A., and Joseph M. Topping, M.D., Division of Pharmacovigilance II (DPV II) of the FAERS cases, foreign and domestic, from the last 10 years for the diagnostic radiopharmaceuticals
- March 2012 Clinical review of Amyvid (florbetapir [NDA 202008, approved agent for PET imaging of the brain to estimate beta-amyloid neuritic plaque density]), Dr. Qi Feng

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM¹

Vizamyl was studied in two single-arm clinical trials in adult patients with a range of cognitive function. Patients received an injection of Vizamyl and had a PET imaging scan. The images were interpreted by five independent readers masked to all clinical information. PET images were reviewed first without, and subsequently with, brain CT or MRI images. Before image interpretation, all readers underwent in-person tutoring on image interpretation.

Study One evaluated 176 Vizamyl PET images from terminally ill patients and compared the results to post-mortem assessments of cerebral cortical neuritic plaque density in patients who died during the study. Readers evaluated the images as positive or negative. The final overall image assessment was compared to the autopsy findings.

The median age of the patients was 82 years (range 47 to 98 years) and 57% of the patients were female. Forty-four patients had no cognitive impairment, 135 had dementia, no patients had mild cognitive impairment (MCI), and one patient had memory loss of unspecified nature. Sixty-nine patients died during the study; 68 had cerebral cortical amyloid status determined (43 positive and 25 negative) and were included in the analysis. The time interval between the Vizamyl scan and death ranged from 0 to 13 months, with a median of 2.6 months, and was less than one year for 66 patients and between 12 to 13 months for 2 patients.

In Study Two, the effectiveness of an electronic training program for Vizamyl image orientation and interpretation was evaluated using Vizamyl PET images across subjects with different cognitive abilities who had participated in earlier studies. Inter-reader reproducibility of image interpretation was assessed using images from subjects with histopathology results (68 patients who underwent an autopsy and 36 known or suspected normal pressure hydrocephalus patients with in vivo brain biopsy) and without histopathology results (28 cognitively normal volunteers 55 years or above, 80 patients with amnesic mild cognitive impairment, 33 subjects with probable AD), and 31 young healthy volunteers. Additionally, intra-reader reproducibility was assessed from 29 images (10%). Among the 276 subjects, the median age was 72 years (range 20 to 95), 136 were females, and 251 were Caucasian.

Among patients who underwent autopsy (n=68; 43 positive and 25 negative based on histopathology), the median (and range) of correct read results, false negatives, and false positives were: correct reads 61 (range, 56, 62), false negatives 4 (1, 4), false positives 3 (2, 11), respectively, for in-person training (Study One); and were 60 (55 to 61), 3 (3 to 6), 4 (2 to 10), respectively, for electronic media training (Study Two). Between the two readings for each of the 29 duplicate patient images, one of the five readers had complete agreement for all 29 images, two readers had discordant reads for a single image, and three readers had discordant reads for two images. For a sub-group of 8 images from

¹ Overview of clinical program adapted from FDA summary in draft Vizamyl labeling, June 6, 2013.

patients with amnesic mild cognitive impairment, all five readers had complete agreement for all duplicate images.

3.2 SAFETY CONCERNS

Flushing, (experienced by 2% of patients), increased blood pressure (1%), nausea (1%), and dizziness (1%) were the most frequently occurring adverse events reported in the clinical trials for flutemetamol F 18. The FDA clinical reviewer identified 3 events to be sufficiently concerning for inclusion in the *Warnings and Precautions* section of the draft labeling; these events are hypersensitivity reactions, image interpretation errors, and risk from exposure to radiation.

One serious adverse event, a case of hypersensitivity, occurring during clinical study was attributed to flutemetamol F 18 by the FDA clinical reviewer. A patient experienced flushing, shortness of breath, and chest pressure within minutes of receiving flutemetamol. The patient recovered after receiving a dose of epinephrine.

Flutemetamol increases patients' cumulative exposure to radiation. Risk of radiation exposure is listed in the *Warnings and Precautions* section of the draft labeling.

Error in interpretation of the PET imaging was noted in the clinical trial data, when test results from PET imaging with flutemetamol were compared to autopsy evidence of neuritic plaque density. Error in interpretation of the PET imaging after receiving flutemetamol is a risk listed in the draft *Warnings and Precautions* section of the labeling.

Reviewer Comments: The risk of error in interpretation of the PET imaging and risk of cumulative radiation exposure are also noted in the labeling for florbetapir F 18, a radiodiagnostic approved for PET imaging to estimate beta-amyloid neuritic plaque density.

3.3 TRAINING PROGRAM USED DURING CLINICAL DEVELOPMENT

In March 2011, the agency issued a complete response letter for florbetapir F 18. The letter required that a training program be developed to teach PET scan readers how to accurately and consistently read the scans, and that readings of the F 18 images be comparable in reliability to that of an autopsy.

Study 1 submitted for flutemetamol F 18 was conducted with in-person training for readers to evaluate the PET images using flutemetamol F 18. The applicant for flutemetamol F 18 developed an electronic training program to provide readers with the ability to estimate the brain beta-amyloid neuritic plaque density and to evaluate the scans as positive or negative based on the estimate of brain beta-amyloid neuritic plaque density. The reading of the brain images are performed independently of the clinical presentation of the patients whose scan is being read. Study 2 was conducted with readers who had received training via the electronically administered training program.

4 DISCUSSION

Flushing, (experienced by 2% of patients), increased blood pressure (1%), nausea (1%), and dizziness (1%) were the most frequently occurring adverse events reported in the clinical trials for flutemetamol F 18. One case of hypersensitivity was reported in the clinical trial data. A patient experienced flushing, shortness of breath, and chest pressure within minutes of receiving flutemetamol. The patient recovered after receiving a dose of epinephrine. The draft *Warnings and Precautions* section of the labeling lists the potential for anaphylactoid reactions based on this case, a risk for misinterpretation of the PET images enhanced with flutemetamol F 18, and a risk from cumulative radiation exposure. These risks appear to be appropriately handled with labeling; these risks do not appear to require that a REMS be implemented to ensure that the benefits of flutemetamol F 18 outweigh these risks.

The applicant has developed a training program for readers of PET scans performed with flutemetamol F 18. This training program is to ensure the efficacy of scanning for brain beta-amyloid neuritic plaque density, not for a safety concern. A REMS is not needed to provide this training.

In November 2012, the Division of Pharmacovigilance II (Michael E. Kieffer, Pharm.D., M.A., Safety Evaluator, and Joseph M. Tinning, M.D., M.P.H., R.Ph., Medical Officer) conducted a review of reports in the FDA Adverse Event Reporting System (FAERS) for radiodiagnostic agents, including florbetapir F 18 (Amyvid), approved by the FDA seven months earlier. Dr Kieffer and Dr. Tinning did not find any adverse event reports for Amyvid. Florbetapir F 18 is approved without a REMS.

5 CONCLUSION/RECOMMENDATION

At this time, there are no safety concerns for flutemetamol F 18 requiring a REMS. Should this product be approved, it appears that labeling alone will be sufficient to relay safety concerns for this product.

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/s/

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