CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204677Orig1s000

SUMMARY REVIEW

3/19/2014

SUMMARY REVIEW ADDENDUM

NDA	204677
Applicant Name	Piramal Imaging
Date of Submission	12/21/2012
PDUFA Goal Date	3/21/2013
Proprietary Name	Neuraceq
Established name	Florbetaben F 18
Reviewer	Libero Marzella MD, PhD

OVERVIEW

The purpose of this addendum is to summarize the evidence supporting the conclusion that the interpretation of Florbetaben F 18 PET scans does not importantly differ between subgroups defined by gender, race, or age. Similarly these demographic criteria did not affect the interpretation of scans obtained with Florbetapir F18 (NDA202008) or Flutemetamol F18 (NDA 203137). The clinical and statistical reviews are in general agreement with this interpretation (see summary data below). The blinded reader image manuals, the literature and the labeling do not describe important differences in image interpretation by these demographic factors. The literature does not report demographic differences in the distribution of amyloid in the brain based on these demographic factors.

Studies in the three NDAs have shown that the regional distribution of beta amyloid in brain scans parallels the distribution observed by histopathology. The summary tables below illustrate this important finding; the tables are reproduced from the statistical review of study PT01 (NDA 202008) performed by Dr. Lan Huang. In addition reader's performance using a clinically applicable read is also shown

The products' labeling cautions to interpret the images in the absence of clinical information and appropriately does not cite the lack of impact of demographics on image interpretation

SUMMARY

<u>NDA 202008</u>

Table 7 shows that across all the brain regions of interest there is a similar correlation between a semiquantitative visual read of the Florbetapir F18 PET scans and quantitative histopathology. Table 18 shows that the correlation between a global visual read and histopathology is equally good by gender. Similar data are available by race and age.

Table 7: Spearman correlation between the semi-quantitative visual blinded read and quantitative IHC measures by region (35 subjects with autopsy)

Region	Spearman's rho 95% CI
Frontal cortex	0.71 0.48,0.84
Temporal cortex	0.68 0.44,0.82
Precuneus	0.76 0.56, 0.87
Parietal cortex	0.72 0.50, 0.84
Anterior Cingulate	0.75 0.54,0.84
Posterior Cingulate	0.68 0.43, 0.82

Table 18: Spearman correlation of IHC and semi-quantitative visual read (reader 1, 2, 3, and median read) measured globally by gender

Gender Male	Corr 95% CI
IHC vs. median read	0.78 (0.47, 0.91)
IHC vs. read from reader 1	0.63 (0.21, 0.84)
IHC vs. read from reader 2	0.82 (0.55, 0.93)
IHC vs. read from reader 3	0.70 (0.32, 0.87)
Gender Female	
IHC vs. median read	0.77 (0.44, 0.91)
IHC vs. read from reader 1	0.80 (0.50, 0.92)
IHC vs. read from reader 2	0.71 (0.32, 0.88)
IHC vs. read from reader 3	0.60 (0.15, 0.83)

Analyses of reader's performance in interpretation of Florbetapir F 18 scans also show no differences in demographic subgroups. The level of agreement among the readers for image interpretation in study PT01 is shown in Table 11.

Table 11: Agreement by demographics (151 subjects)

	N	kappa	Percent agreement (%)(sum in row as 100%)		
			3 readers agree	4 readers agree	5 readers agree
Age					
<65	34	0.92 (0.81, 1)	3	3	94
>=65	117	0.81 (0.75, 0.87)	8	13	79
Gender					
Male	76	0.81 (0.76, 0.86)	5	14	80
Female	75	0.85 (0.78, 0.92)	8	7	85
Ethnicity					
Hisp or Lat	20	0.84 (0.78, 0.88)	5	10	85
Non-Hisp or Lat	131	0.83 (0.78, 0.92)	7	11	82
Race					
Caucasian	141	0.83 (0.78, 0.88)	7	11	82
Black or A -A	7	1 (0.76, 1)	0	0	100
Other	3	0.72 (0.36, 1)	0	33	67

NDA203137

The performance of the readers who interpreted the Flutemetamol F 18 scans in study GE067-021 did not differ across demographic subgroups such as gender and age. Table 7 from Dr. Huang's review shows the sensitivity and specificity by gender for each of five readers who interpreted the scans. The table also lists subjects with truth standard based on autopsy and biopsy or autopsy alone.

Table 7: Sensitivity (sen) and specificity (spe) by gender (in %); pos for positive cases, neg for negative cases

104 subjects (68 autopsy and 36 biopsy)					68 autopsy subjects			
reader	n=pos+neg	gender	sen	spe	n=pos+neg	gender	sen	spe
1	57=28+29	M	93	69	33=21+12	M	90	75
	47=23+24	F	96	67	35=22+13	F	95	69
2	57=28+29	M	86	83	33=21+12	M	86	92
	47=23+24	F	100	75	35=22+13	F	100	77
3	57=28+29	M	93	86	33=21+12	M	90	92
	47=23+24	F	87	92	35=22+13	F	91	85
4	57=28+29	M	93	72	33=21+12	M	90	58
	47=23+24	F	96	71	35=22+13	F	95	62

5	57=28+29	M	82	97	33=21+12	M	81	100
	47=23+24	F	87	92	35=22+13	F	91	85

Table 8 is also reproduced from DR. Huang's review. The table shows that there are no important differences in the agreement among readers across gender and age subgroups

Table 8: Reader agreement evaluation by gender and age

Subject Group by gender and age group	**Positive Scans, n[a]**	**Kappa (95% CI)**	**Percent of Scans with Inter-reader**		
			3 of 5 readers	**4 of 5 reader**	**5 of 5 readers agreed**
Gender: Male (n=140)	57	0.81 (0.76, 0.86)	4	1	79
Gender: Female (n=136)	80	0.84 (0.78, 0.89)	7	1	83
age>=65 (n=198)	116	0.83 (0.79, 0.87)	5	1	84
Age<65 (n=78)	21	0.74 (0.67, 0.81)	5	1	78

[a] Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of subjects listed in the first column.

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Summary data for the Florbetaben F 18 histopathology new read study further supports the assessment that gender, race ,and age are not important factors in the interpretation of PET scans obtained using beta amyloid imaging agents.

Table 1: Reader agreement evaluation by gender, race, and age groups

Subject Groups	Positive Scans, n[a]	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agreed	4 of 5 readers agreed	5 of 5 readers agreed
Gender					
Male (n=47)	33	0.71 (0.62, 0.80)	11	11	79
Female (n=35)	24	0.78 (0.67, 0.88)	3	20	77
Race					
White (n=54)	37	0.76 (0.68, 0.85)	9	9	81
Asian (n=28)	20	0.71 (0.59, 0.82)	4	25	71
Age group					
<=65 (n=9)	5	0.91 (0.70, 1.00)	0	11	89
>65 (n=73)	52	0.71 (0.64, 0.79)	8	15	77
<=75 (n=25)	16	0.79 (0.67, 0.92)	12	4	84
>75 (n=57)	41	0.72 (0.64, 0.80)	5	19	75

[a] Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of subjects listed in the first column.

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/s/

LIBERO L MARZELLA
03/19/2014

Summary Review for Regulatory Action

Date	2/28/2014
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	204677
Applicant Name	Piramal Imaging
Date of Submission	12/21/2012
PDUFA Goal Date	3/21/2013
Proprietary Name / Established (USAN) Name	Neuraceq Florbetaben F 18
Dosage Forms / Strength	Solution for Injection/ 50 to 5000 MBq per mL at calibration time
Indications	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.
Action Recommended	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Ye MD
Statistical Review	Lan Huang PhD
Pharmacology Toxicology Review	Sunny Awe PhD
CMC Review/OBP Review	Ann Marie Russell PhD
Microbiology Review	Erika Pfeiler PhD
Clinical Pharmacology Review	Christy John PhD
OPDP	Emily Baker
OSI	Lee Jong Hoon MD
CDTL Review	Alex Gorovets MD
OSE/DMEPA	Kevin Wright PharmD
OSE/DRISK	Amarilys Vega MD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI= Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

The objective of this review is to summarize my assessment of the major issues regarding the approvability of the application. Florbetaben F 18 is a radioactive diagnostic agent proposed for use for Positron Emission Tomography imaging of the brain for visualization of β amyloid plaque.

The clinical trial designs and efficacy endpoints for radiopharmaceutical imaging drugs that target β amyloid were established at meetings of the Peripheral and Central Nervous System Drugs Advisory Committee held on October 23, 2008 and on January 20, 2011. The efficacy trials of the β amyloid imaging agents have two main objectives. The trials are designed to demonstrate that the accuracy (sensitivity and specificity) and the reproducibility of the image interpretation methods are acceptable.

The first clinical development objective for β amyloid imaging agents (assessment of accuracy) is achieved by single-arm studies in terminally ill patients with and without a cognitive disorder who consent to undergo a post-mortem examination of the brain. These studies are designed to compare β amyloid burden in PET scans to the β amyloid burden in post-mortem brain sections examined histopathologically. The limitations of these studies include low accrual, variable interval between in life and post-mortem assessments, and a patient population skewed towards more advanced disease. The PET images are randomized and are interpreted independently by multiple trained radiologists (readers) who are blinded to clinical information. Generally the readers assess β amyloid burden in specific brain regions and make a final binary interpretation of the scan as either positive or negative. Negative scans generally show more radioactivity signal in the white matter than in the gray matter and show distinct grey-white contrast. Positive scans show loss of gray-white contrast and or increased cortical gray matter signal. In these studies the brain histology is assessed centrally in a standardized manner by experienced pathologists who are blinded to the interpretation of the PET scans. These standard procedures generally minimize variability of the interpretations and enhance the verifiability of the reading process.

The second clinical development objective for β amyloid imaging agents is the assessment of reproducibility of image interpretations and the adequacy of a reader training procedure. For this testing subjects without cognitive impairment (e.g. healthy young volunteers), mild cognitive impairment (MCI) or dementia receive a radiopharmaceutical injection and are scanned. These studies are designed to assess inter- and intra-reader agreement in image interpretation of scans obtained in subjects with a range of cognitive function. Reader performance in patients with a truth standard (post-mortem) is also determined. Given the importance of image reproducibility, it is generally recommended that in clinical use readers successfully complete an electronic-based training program developed and provided by the manufacturer.

Other objectives that play a supportive role in the clinical development program for β amyloid imaging agents include proof of concept studies such as *in vitro* binding studies of the drug to

post-mortem human brain homogenates prepared from patients with Alzheimer's disease (AD) or to synthetic fibrillar amyloid. These studies estimate the dissociation constant of the investigational imaging agent. Studies were performed to evaluate the binding of florbetaben F18 to β amyloid plaques in post-mortem AD brain sections by autoradiography and to correlate it with immunohistochemical and Bielschowsky silver stains. Proof of concept was also obtained from studies that compared β amyloid burden in virtual brain slices from PET scans and β amyloid burden in post-mortem brain sections examined histopathologically.

The clinical development of florbetaben F 18 was in general similar to the approach used for florbetapir F 18 (Amyvid) and for flutemetamol F 18 (Vizamyl), respectively the first and second radiopharmaceutical approved for use in PET imaging of the brain to estimate the density of β amyloid neuritic plaque.

A complete response action for the application was anticipated because the efficacy data in the initial NDA submission were not adequate to establish the effectiveness of florbetaben F 18 as an amyloid imaging agent. Study 14595 had achieved its primary efficacy endpoint and was acceptable as a method validation study. However, study 16043 had only met its primary efficacy endpoint of reader agreement and had failed to meet the key secondary endpoint of specificity of the reader's interpretations. The Division recommended that the applicant conduct a new reader study of all the cases in study 14595 for whom standard of truth data were available.

On November 22, 2013 the applicant submitted to the NDA the complete report of a new clinical study. The clinical and statistical reviewers determined that the study protocol was acceptable, the study results and the data sets were reviewable and that, if verified, the results could address the clinical and statistical deficiencies in the initial NDA. For these reasons the Division designated the submission as a major amendment and extended the PDUFA review goal date.

2. Background

Alzheimer's disease is a neurodegenerative disorder characterized by β amyloid accumulation in the brain. Amyloid is an abnormal extracellular aggregate of insoluble protein fibrils with staining properties that are used for histopathologic diagnosis.

Alzheimer's disease usually manifests in middle or late life with progressive development of cognitive dysfunction, behavioral symptoms, and difficulty performing activities of daily living. Evaluation of patients with cognitive dysfunction may be aided by laboratory testing including imaging; however a definitive diagnosis can only be made by pathological evaluation of brain at post-mortem.

Pharmacology proof of concept studies show that florbetaben binds to β amyloid in human brain homogenates. Following intravenous injection florbetaben F 18 diffuses into the brain. Over time, the blood flow reduces overall brain florbetaben F 18 signal with differential retention of the signal in cortical areas that contain β amyloid aggregates. The F 18 isotope

produces a positron signal that is detected by a PET scanner. Differences in signal intensity between brain regions form the basis of image interpretation methodology.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer Dr. Russell in the December 13, 2013 review regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding CMC issues.

At the time of the initial CMC review the justification for organic impurity acceptance criteria proposed in the (b) (4) specifications was not adequate. The revised (b) (4) specifications are now acceptable. The acceptance criteria for all but two of the specified impurities are now within the ICH Q3A qualification limit (0.15%) and the acceptance criteria of the two specified impurities which exceed that limit have been justified as (b) (4)

I concur with the microbiology reviewer, Dr. Erika Pfeiler, that the product quality is acceptable from the microbiologic perspective and with the reviewer's approval recommendation.

Manufacturing site inspections were acceptable to the Office of Compliance. The (b) (4) stability data provided are sufficient to support the proposed (b) (4) retest period.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer Dr. Awe in a review dated August 22, 2013 that there are no outstanding issues that preclude approval.

Safety pharmacology studies showed that florbetaben did not induce cardiovascular, renal, pulmonary or central nervous system alterations. Acute and expanded single-dose toxicity studies were conducted in rats and rabbits; repeat-dose toxicity studies were conducted in rats and dogs over a period of 4 weeks followed by a recovery period of 4 weeks. Acceptable NOAEL were established in all these species; injection site tolerance was acceptable. Studies to assess mutagenic potential of florbetaben were negative.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.
Dr John referenced his previous findings (August 22, 2013) that dose finding studies are acceptable. In particular the selection of a dose of radioactivity of 300 MBq corresponding to a mass dose of less than 30 mcg is acceptable to the reviewer based on results of dosimetry

studies confirming that organ radiation exposure is within acceptable limits and based on adequate diagnostic performance. Florbetaben F 18 crosses the blood brain barrier and shows differential retention in brain regions that contain β amyloid deposits. Following florbetaben F 18 injection stable signal suitable for imaging begins in approximately 45 to 130 minutes.

6. Clinical Microbiology

This section is not applicable to this NDA.

7. Clinical/Statistical-Efficacy

I concur with the approval recommendations by the statistical reviewer (Dr. Lan Huang) and by the clinical reviewer (Dr. Brenda Ye) that the new data submitted as a major amendment have been verified and provide the confirmatory evidence of efficacy lacking in the initial NDA submission. The reader is also referred to the Cross Discipline Team leader review by Dr. Alexander Gorovets for a summary of the issues identified in the initial NDA submission.

The initial NDA application relied on two efficacy studies designated here as: 1) the "histopathology study" [#14595] and 2) the "pooled read" study [#16043].

1. The histopathology study enrolled end-of-life patients who underwent a florbetaben F18 PET scan. The primary analysis population consisted of 31 patients who underwent post-mortem brain histopathology. The β amyloid neuritic plaque burden on Bielschowsky silver stained brain sections (and other stains) was assessed according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria by a consensus panel blinded to clinical and PET scan data. For the subject level SoT, if in any of the six brain regions β amyloid neuritic plaques were more than sparse, the subject was classified as positive; if in none of the brain regions the β amyloid neuritic plaques were assessed as being more than sparse, the subject was classified as negative.

   The histopathology study met its primary objective of concept validation by demonstrating that blinded readers could reliably assess amyloid burden in specified brain regions (n=246) in the PET scans as verified by histopathology of the same brain regions. The study achieved a regional sensitivity of 77% (66%, 89%)[a] and a regional specificity of 94% (89%, 100%).

   The histopathology study also arguably met a secondary objective of assessing reliability of global brain amyloid burden assessment as performed by a new set of blinded readers who were in-person trained using the practice-applicable method for image interpretation. However, the clinical and statistical reviewers viewed these analyses as exploratory primarily because of issues with the definition of the truth standard. For this reason the reviewers recommended that these results be confirmed.

2. The pooled read study was based on brain scans (n=454) obtained from completed studies and included cognitively normal young or older volunteers and patients with post-mortem brain histopathology, AD or non-AD dementias, or mild cognitive impairment.

   The pooled read study met its primary objective of agreement across five readers trained using an electronic training tool with a kappa statistic of 0.80 (0.77, 0.83). The statistical reviewer-verified outcomes are shown in Table 1. Reader agreement across patient subgroups (e.g. patients with MCI) did not vary from agreement in the overall group. Demonstration of this level of consistency is an important study achievement because it is not possible to verify the accuracy of the reads in patients without a truth standard.

Table 1: Reproducibility of Scan Results among Readers in Various Subject Groups

Subject Group by Cognitive Status and Standard of Truth (SoT)	Positive Scans median	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agreed	4 of 5 readers agreed	5 of 5 readers agreed
All subjects (n=454)	212	0.80 (0.77, 0.83)	6	15	78
Subjects without SoT (n=394)	175	0.80 (0.77, 0.83)	6	15	79
Subjects with SoT (n=60)	37	0.75 (0.67, 0.83)	10	15	75
AD (n=176)	139	0.77 (0.72, 0.81)	7	10	83
MCI (n=50, all without SoT)	28	0.88 (0.75, 0.92)	0	20	80

   An important secondary objective of the pooled read study was the demonstration of acceptable accuracy. The study met its sensitivity threshold with point estimates ranging from 78% to 90% and lower bound of 95% CI ranging from 62% to 76% among the five readers. However, the study did not meet its endpoint of specificity (range 63% to 92%; lower bound 95% CI 41% to 73%).

   Despite the study's success in meeting its primary endpoint of agreement, the absence of acceptable accuracy (due to low specificity) undermined the strength of the agreement outcome and made a confirmatory study of florbetaben F 18 accuracy necessary.

The Division informed the applicant of the need to confirm the accuracy of florbetaben F18 by a re-read of all the images obtained in the histopathology study (14595) for which a truth standard was available. The applicant performed the study and the submission of the study results and datasets triggered a major amendment and an extension of the PDUFA review timelines. The study is designated here as: 3) "Histopathology new read study [FBB-01_01_13].

3. The histopathology new read study enrolled no new subjects but analyzed images from 82 subjects from study 14595 with postmortem histopathology. The images were

interpreted by five blinded independent readers trained using an electronic training program.

The reviewers verified that the study met its primary objective of accuracy. The lower bounds of the 95% confidence intervals (CIs) for sensitivity were > 0.7 for all five readers and the lower bounds of the 95% CIs for specificity were > 0.5 for three readers. However, two readers had inadequate performance for specificity (the lower bounds of the CIs were 28% and 37%). Reuse of images from study 14595 raised some concern about potential for reader interpretation bias. Finally the inter- and intra-reader agreement measures were acceptable.

I concur with the final assessment by the clinical and statistical reviewers that the cumulative evidence from the three efficacy studies summarized above shows that florbetaben F 18 is effective for the proposed clinical use.

4. Safety

I concur with the assessment by the clinical and by the CDTL reviewers (Drs. Ye and Gorovets) that the safety of florbetaben F 18 is acceptable. The florbetaben F 18 database consists of 872 subjects. No deaths or serious adverse reactions have been attributed to the drug. The most common adverse reactions were injection site reactions and headaches.

5. Advisory Committee Meeting

The product was not referred for review to an AC because the regulatory path for this imaging indication has been extensively discussed at previous ACs and this application did not raise new regulatory issues.

6. Pediatrics

This application triggered the Pediatric Research Equity Act as a new indication, active ingredient, route of administration, dosing regimen and dosage form. At a July 10, 2013 meeting the Pediatric Review Committee agreed with the Division to grant a full waiver of studies in pediatric patients because studies are impossible or highly impracticable because AD does not exist in children.

7. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

I agree with Dr. Vega's assessment (OSE/DRISK) that the main safety concern associated to the use of florbetaben is the risk of radiation and that a REMS is not necessary to manage the risk.

The labeling concerns cited by the FDA OPDP and DMEPA reviewers (E. Baker and K. Wright) and have been addressed in the revised labeling.

Four sites were inspected by the Office of Scientific Investigations in support of this NDA: three contract research organization sites (imaging, pathology, and study monitoring) and one representative clinical investigator site. As reported by Dr. John Lee (August 30, 2013), deficiencies with the potential to adversely affect data reliability were not observed.

8. Labeling

Labeling negotiations were ongoing at the time this review was filed. Most major issues in the prescribing information including claims for diagnostic (b) (4) utility of florbetaben F18 had been resolved. It was anticipated that full agreement would be reached on remaining relatively lesser labeling issues. The most notable of these concerns was (b) (4)

To facilitate readability the efficacy data were grouped and presented as Study A-C in clinical studies section of the prescribing information. Given the importance of reproducibility of the image interpretation, the labeling will reference the need to successfully complete a training program before interpreting florbetaben F 18 scans.

9. Decision/Action/Risk Benefit Assessment

I concur with the unanimous recommendation by the consultants and primary review disciplines that this application be approved.

The demonstrated accuracy (sensitivity and specificity) and reproducibility of this imaging test provide the needed evidence for the proposed use for the estimation of β amyloid neuritic plaque density in the brain in adults with cognitive impairment undergoing evaluation for AD or other causes of cognitive decline.

Weaknesses in the efficacy data include poor specificity performance by two of the five readers in study 3, limited number of scans available from patients with MCI (an important group in which this scan will be used). As applicable to the other β amyloid imaging agents an important limitation of florbetaben F 18 is the lack of diagnostic or prognostic value for AD or AD development.

With regard to safety, florbetaben F 18 is not pharmacologically active and is administered in microdose (<30 mcg) quantity. No serious or severe adverse reactions to the imaging agent were observed in the clinical studies. Exposure to radioactivity is associated with malignancy and the labeling carries this warning; however the risk from the low exposure to F 18 (300 MBq) is difficult to assess. Patients are to be instructed to inform their healthcare provider if they are pregnant or breastfeeding and patients who are breastfeeding are to be instructed to use alternate infant nutrition sources for 24 hrs after receiving florbetaben F 18.

The risk of image misinterpretation of β amyloid scans is recognized and is due mainly to the qualitative nature of the assessment of tracer uptake in the cortical gray matter relative to adjacent white matter. To mitigate this risk the labeling contains a warning about interpretation errors and includes the requirement that images should be interpreted only by readers who successfully complete electronic media- or in-person training provided by the manufacturer.

I conclude that the overall bisk benefit for florbetaben F 18 is favorable. No Postmarketing Risk Evaluation and Mitigation Strategies or other Postmarketing Requirements and Commitments are needed.

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/s/

LIBERO L MARZELLA
02/28/2014