

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-119

MEDICAL REVIEW

Memorandum

Date: August 15, 2007

From: Karen Weiss, M.D. Deputy Director, OODP

Subject: NDA #22-119, Ammonia N 13 Injection

To: File

Ammonia N 13 is a positron emitting radiopharmaceutical. The application under consideration is for use in patients with suspected coronary artery disease to image the myocardium under rest and pharmacologic stress conditions. The history of radio-isotope approvals for use in positron emitting tomography (PET) is somewhat unusual. The Agency issued a finding that certain PET drugs produced under specified conditions can be considered safe and effective (see FR vol. 65, No. 48, March 10, 2000). The March 2000 FR notice specified FDA procedures for approval of such agents, and invited manufacturers to submit applications for approval per draft guidance ("PET drug Applications-Content and format for NDA's and ANDA's"). The agency also reviewed the published literature as relevant for certain PET drugs, including Ammonia 13, and stated...."[b]ecause of the publicly available safety and effectiveness data documenting the product's use cited in this review, safety and effectiveness requirements of section 505(b)(2) of the act (21 USC 355(b)(2)) and part 314 (21 CFR part 314) for this product and this use may be met by citing the docket number (Docket No.98d0266/ref0001w) of this review. "

The sponsor for the present application is Feinstein Institute for Medical Research. The sponsor submitted this application in accordance with Agency guidance. It contained no primary clinical data, but rather reference to the Agency's review of safety and effectiveness see <http://www.fda.gov/cder/regulatory/pet/ammonfinal.htm> and additional literature that became available subsequent to the Agency review. The primary medical reviewer assigned to this application considered the available additional literature (published 2000-2007) and concluded that the information continues to support the safety and effectiveness of Ammonia N 13. The dose of Ammonia N 13 injection is 10-20 Mci. Of note, and based on the available literature, this agent is considered acceptable for use in pediatric populations to assess myocardial perfusion, but there are no data to support its use in pregnant women and no information on drug-drug interactions.

I support the medical officer, MTL, and acting division director recommendations to approve this product. I have reviewed the labeling (in PLR format) and concur with the final version.

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/s/

Karen Weiss
8/15/2007 12:05:26 PM
MEDICAL OFFICER

ACTING DIVISION DIRECTOR'S REVIEW MEMORANDUM

NDA: 22-119
DRUG: Ammonia N 13 Injection
TRADENAME: Ammonia N 13 Injection
FORMULATION: Solution in vials with designated quantities of radioactive ammonia
ROUTE: Intravenous administration
DOSE: 0.138 to 1.387 GBq (3.75 - 37.5 mCi/mL)
SPONSOR: Feinstein Institute for Medical Research
SUBMITTED: October 16, 2006
PDUFA DUE DATE: August 24, 2007
DD MEMO COMPLETED: July 20, 2007
DD MEMO PREPARERS: Dwaine Rieves, MD, Acting Division Director
Division of Medical Imaging and Hematology Products

SPONSOR'S PROPOSED INDICATION:

"Ammonia N 13 Injection is a positron emitting radiopharmaceutical indicated for diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease."

RELATED REVIEWS:

Clinical: Cynthia Welsh, M.D.; Libero Marzella, M.D., Ph.D.
Chemistry: Ravindra Kaslival, Ph.D., Ravi Harapanhalli, Ph.D. and Eldon Leutzinger, Ph.D.
Microbiology: Anastasia Lolas, Ph.D.
Project Manager: Thuy Nguyen, M.P.H.
Advisory Committee: None

RECOMMENDED REGULATORY ACTIONS:

Approval with no post-marketing commitments:

The sponsor submitted this NDA in a manner consistent with the FDA guidance document entitled, "Guidance for Industry: PET Drug Applications--Content and Format for NDAs and ANDAs: Fludeoxyglucose F 18 Injection, Ammonia N 13 Injection, Sodium Fluoride F 18 Injection." The history of PET product regulation is somewhat unusual in that the FDA performed review of published literature to determine, as stated in the guidance, that sponsors did not need to submit clinical data to assess the safety and efficacy of the cited PET products because FDA had performed a review and determined that these products were acceptable for marketing. Indeed, FDA published its reviews of the published data and provided draft text for labels as well as templates for submissions of the NDAs. These activities followed a requirement within the 1997 PDUFA legislation that mandated FDA develop procedures to approve PET products.

Consequently, this NDA did not contain clinical data and the extent of the clinical review was limited to an examination of the literature published following FDA's review (1999) and comments regarding the FDA review document. As described within Dr. Cynthia

Welsh's review memorandum, the published clinical data continue to support the safety and efficacy of Ammonia N 13 for use in the cited indication. Dr. Welsh noted, however, that the product label should be somewhat modified from the published FDA template since she detected a few errors in data interpretation. Consequently, the description of the clinical data supporting efficacy are somewhat modified from the template text described in published FDA information. The detected errors did not alter the interpretation of acceptable safety and efficacy.

Of note, the FDA had previously determined that Ammonia N 13 had demonstrated safety and efficacy in pediatric patients and the proposed product label carries a relatively solid statement supporting use of the product in pediatric patients (text identical to published FDA advice).

Overall, the manufacturing and facilities review of the NDA data were substantively the only new information submitted and the FDA review teams found that the information was sufficient to support approval.

I agree with all review teams in approval of the application. I have requested a minor clarification of some of the labeling text and anticipate these items will be readily clarified such that the application can be approved.

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Rafel Rieves
7/20/2007 07:02:09 PM
MEDICAL OFFICER

May 14, 2007

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY

Secondary Clinical Review

NDA	22-119
Established Name	Ammonia N-13
(Proposed) Trade Name	none
Therapeutic Class	Diagnostic Radiopharmaceutical
Applicant	Feinstein Institute for Medical Research
Dosing Regimen	10-20 mCi at rest and stress
Indication	Myocardial perfusion imaging
Intended Population	Patients with known or suspected coronary artery disease
Reviewer Name	Louis Marzella M.D., Ph.D.

Recommended Regulatory Action

The secondary reviewer agrees with the finding by Dr. Cindy Welsh (primary clinical reviewer) that this NDA contains no new clinical data. Furthermore, the recent scientific literature supports the safety and efficacy of ammonia N13 PET imaging of the myocardium to evaluate myocardial perfusion under rest or pharmacologic stress in patients with suspected or existing coronary artery disease.

The secondary reviewer agrees with Dr Welsh's labeling review and with her recommendation to revise the label to reflect the inability to draw inferences about the diagnostic performance of ammonia N 13 PET imaging relative to the truth standard of coronary angiography.

Recommended Postmarketing Actions

Given the lack of material new information on safety or efficacy no risk modification steps or new studies are recommended.

Review Procedure

The secondary reviewer read the medical officer's primary review, the FR notice and FDA's original review establishing the safety and efficacy of the product and sample labeling. The secondary reviewer also read the abstracts obtained in a search of the recent literature and evaluated the main articles on which the finding of efficacy was based.

Summary of Clinical Findings

As discussed by Dr. Welsh, the Agency made a finding of the safety and efficacy of ammonia N13 PET imaging for the measurement of rest and stress myocardial perfusion based on its review of the literature. The Agency made its findings public in an FR notice in 2000. This is the first NDA for ammonia N13 that is based on the Agency's determination. The submission contains no new clinical data.

Literature Review

Dr. Welsh conducted a review of the scientific literature published after the original FDA review and concluded that no new material efficacy information emerges from the studies. The secondary reviewer agrees with that assessment.

With regard to efficacy in adults, the published articles provide evidence of continued use of ammonia N13 for measurement of myocardial perfusion in clinical studies of adults with and without coronary artery disease. A number of small descriptive studies in general support the efficacy of ammonia N 13 in the adult indicated population. None of the reports raise concerns about lack of efficacy for the indicated use. Other reported studies explore several potential uses of ammonia N13 with PET or SPECT imaging. These exploratory uses include: assessment of global myocardial function (e.g. cardiac output, left ventricular ejection fraction); visualization of other organs (e.g. brain, kidneys); assessment of physiologic or pathologic processes (e.g. tissue metabolism, malignancies); combined use with CT. No conclusions can be drawn from these small exploratory studies.

With regard to efficacy in children, small pediatric studies of ammonia N13 in infants and children with suspected coronary artery abnormalities (including a comparative truth standard study) have been reported and support the efficacy of the product in the indicated pediatric population.

The secondary reviewer agrees with Dr Welsh's conclusion that the published literature provides no evidence of safety signals. However in general the quality of the ascertainment of safety cannot be assessed from the published reports. For example the types of clinical assessments and the duration of follow up are not adequately described. Given the potential for the occurrence of serious adverse events in the study population (particularly as a consequence of pharmacologic stress imaging) the reviewers presume that adverse events were either not captured or were judged to be unrelated to the test agent. The secondary reviewer agrees with the recommendation to caution about inferring safety from the lack of reported adverse reactions.

The secondary reviewer notes that the sponsor conducted a literature review at the request of the agency and found no evidence of lack of efficacy or of emerging safety concerns

Review of Medwatch Database

The secondary reviewer notes that a search of the FDA database revealed no reports of adverse reactions from ammonia N13.

Additional Clinical Issues and Labeling Review

Recommended dose of ammonia N13:

The secondary reviewer notes Dr Welsh's clarification that the ammonia N13 dose cited in the FR notice (10 mCi) is not meant as a dosing recommendation. Dr Welsh confirms and the secondary reviewer agrees that the 10-20 mCi dose cited in the sample package insert prepared by FDA is fully supported by the literature.

Diagnostic performance of ammonia N13 PET:

The secondary reviewer agrees with Dr. Welsh's review of the strengths and limitations of the descriptive study by Demer *et al.* (see also NDA review by FDA's statistician Dr. Zalkikar). Dr Welsh argues convincingly that design of the study and the data presented in that paper are not sufficient to support a definitive assessment of the diagnostic sensitivity and specificity of the ammonia N 13 PET. Consequently Dr Welsh makes a reasonable recommendation that the efficacy finding of that study should be presented in a more descriptive fashion in the label.

Recommended Starting time for PET Imaging and Dosimetry Data

The secondary reviewer agrees with the recommendations by the FDA pharmacology reviewer (see Dr. Young-Moon's review) and by the clinical reviewer that the optimal time for imaging after the administration of ammonia N13 be stated consistently as between 10 and 20 min in the label. Similarly the interpretation of numerical differences in dosimetry data between various age groups (presented in Table 1 of the label) is not necessary as the data are descriptive and a restatement of the numbers is redundant.

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/s/

Liberio Marzella
5/22/2007 03:14:54 PM
MEDICAL OFFICER

Rafel Rieves
5/25/2007 08:32:26 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type 22-119
Submission Number 000

Letter Date October 16, 2006
Stamp Date October 25, 2006
PDUFA Goal Date August 24, 2007

Reviewer Name Cindy Welsh
Review Completion Date May 16, 2007
Through Louis Marzella, MD
Acting Deputy, DMIHP
Dwayne Rieves, MD
Acting Division Director, DMIHP

Established Name Ammonia N-13
(Proposed) Trade Name none
Therapeutic Class Diagnostic Radiopharmaceutical
Applicant Feinstein Institute for Medical Research

Priority Designation S

Formulation Intravenous injection
Dosing Regimen 10-20 mCi at rest and stress
Indication Myocardial perfusion imaging
Intended Population Patients with known or suspected
coronary artery disease

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	See FR notice. No new clinical data	9

7.2.2 Description of Primary Clinical Data Sources Used to Evaluate Safety	9
The Office of Surveillance and Epidemiology (OSE) was consulted. The AERS database was searched for safety reports regarding Ammonia N13. None were found.....	9
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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval action for Ammonia N13 for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease based on Federal Register (FR) notice [00N-0553]: Volume 65, Number 48 dated March 10, 2000 and an updated literature review.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No recommendations for risk management are being made at this time.

1.2.2 Required Phase 4 Commitments

No recommendations for phase 4 commitments are being made at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ammonia N13 is an intravenously administered diagnostic radiopharmaceutical for which the applicant is seeking an indication of PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease. The information supporting this new drug application is outlined in the FR notice of March 10, 2000 and is based on a medical and statistical review conducted by the agency at the time of the FR notice that supports the safety and efficacy of Ammonia N13 in adult and pediatric patients. An updated review of the literature from 2000 – 2007 by the applicant and the reviewer continues to support the safety and efficacy of Ammonia N13.

1.3.2 Efficacy

The efficacy of Ammonia N13 is based on literature data as reviewed by the agency. Updated literature review discovered no reason to modify continued support for the efficacy of Ammonia N13 for evaluation of myocardial perfusion. The literature reveals no major trials evaluating

Ammonia N13 PET for evaluation of coronary artery disease. The majority of papers discusses coronary anatomy or evaluates new uses for Ammonia N13 cardiac PET imaging.

1.3.3 Safety

The safety database for Ammonia N13 includes review of the published literature experience and the AERS database. No safety concerns or signals are evident. No published studies were performed specifically addressing the safety of Ammonia N13 nor do studies evaluating its usefulness test for safety signals.

1.3.4 Dosing Regimen and Administration

The label for Ammonia N13 recommends, as supported in the original medical and statistical literature review, a dose range of 10-20 mCi intravenously at both rest and stress. See section 8.1 for details regarding the FR notice dosage.

1.3.5 Drug-Drug Interactions

Based on the reviewed literature, the possibility of interactions with Ammonia N13 Injection with other drugs taken by patients undergoing PET imaging has not been studied. No papers were found that addressed this issue or mentioned any drug interactions.

1.3.6 Special Populations

Based on the reviewed literature, the safety and efficacy of Ammonia N13 Injection in pregnant patients, renally impaired patients, and hepatically impaired patients undergoing PET imaging has not been studied. No papers were found updating or evaluating this statement.

The effects of Ammonia N13 on human breast milk are unknown. Infant formula should be substituted for breast milk for 6 hours (biologic half-life of N13 is about 3 minutes) after administration of Ammonia N13.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ammonia N13 Injection (no trade name) is a diagnostic radiopharmaceutical used intravenously to evaluate myocardial perfusion using PET imaging at rest and pharmacologic stress for patients with existing or suspected coronary artery disease. The dosing regimen is 10-20 mCi intravenously at rest and at stress.

2.2 Currently Available Treatment for Indications

Ammonia N13 is the only PET agent available for evaluation of myocardial perfusion. Three agency approved single photon emission computed tomography (SPECT) agents (Thallium, Cardiolite, and Myoview) are currently available on the market for evaluation of myocardial perfusion.

2.3 Availability of Proposed Active Ingredient in the United States

Due to the short half-life of Ammonia N13 Injection, the drug availability is limited to the manufacturing facility as an on-site cyclotron is required for production.

2.4 Important Issues with Pharmacologically Related Products

Not applicable.

2.5 Presubmission Regulatory Activity

There was no presubmission regulatory activity between the applicant and the agency. The regulatory activity is limited to the FR notice from March 2000 and the Medical and Statistical review performed by the agency in 1999. There were no presubmission meetings.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See CMC review.

3.2 Animal Pharmacology/Toxicology

Not applicable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data used in the review to support approval of Ammonia N13 consist of the original review performed by the agency in 1999, the FR notice published in March 2000, and an updated literature search performed by both the applicant and the reviewer.

4.2 Tables of Clinical Studies

Not applicable.

4.3 Review Strategy

The safety and efficacy of the product was based on literature for support. The original Medical and Statistical review of 1999 that was performed by the Agency and the FR notice published in March 2000 were reviewed. The literature supplied by the applicant was reviewed. The AERS database was searched for safety reports regarding Ammonia N13. A literature search was performed. Biosis, SciSearch on DialogSelect, PubMed, Embase, as well as Cambridge Scientific Abstracts systems were queried for adverse events regarding Ammonia N13. A literature search for reports of clinical studies using ammonia N13 was performed.

4.4 Financial Disclosures

There is no financial arrangement to be disclosed.

5 CLINICAL PHARMACOLOGY

Not applicable. See literature review.

6 INTEGRATED REVIEW OF EFFICACY

The submission contained no new clinical data.

6.1.1 Clinical Microbiology

The microbiology review recommends approval.

6.1.2 Efficacy Conclusions

The agency made a finding of efficacy in 1999 based on its review of the literature. The available information based on literature supports the approval of Ammonia N13 to evaluate perfusion of the coronary arteries in patients with known or suspected coronary artery disease.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Deaths

No deaths.

7.1.1 Other Serious Adverse Events

No serious adverse events.

7.1.2 Dropouts and Other Significant Adverse Events

Not applicable.

7.1.3 Other Search Strategies

7.1.4 Literature reports of Common Adverse Events

No adverse events reported.

7.1.5 Human Carcinogenicity

Studies with Ammonia N 13 Injection have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

7.1.6 Special Safety Studies

Not applicable.

7.1.7 None expected. Human Reproduction and Pregnancy Data

Animal reproduction studies have not been performed with Ammonia N 13 Injection. It is not known whether Ammonia N 13 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ammonia N 13 Injection should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

7.1.8 Assessment of Effect on Growth

Studies have not been performed to assess the effect on growth of Ammonia N 13.

7.1.9 Overdose Experience

Overdoses of Ammonia N 13 Injection have not been reported.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources Used to Evaluate Safety

See FR notice. No new clinical data.

7.2.2 Description of Primary Clinical Data Sources Used to Evaluate Safety

The Office of Surveillance and Epidemiology (OSE) was consulted. The AERS database was searched for safety reports regarding Ammonia N13. None were found.

A literature search was performed. Biosis, SciSearch on DialogSelect, PubMed, Embase, as well as Cambridge Scientific Abstracts systems were queried for adverse events regarding Ammonia N13. No citations were found.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A. The applicant of NDA 22119 N13 ammonia has requested a dose of 10-20 mCi. There was a question of this dose exceeding the 10 mCi dose listed in the March 2000 FR notice:

The literature indicates that after a total intravenous dose of approximately 25 mCi of ammonia N 13 injection, the critical target organ (bladder wall) absorbs only 1.28 rems. Therefore, a 10-mCi dose of ammonia N 13 injection appears to pose a relatively low risk to adult patients.

The clinical reviewer's interpretation of the above statement excerpted from the FR Notice is that the intent was not to limit or dogmatically state that dose of the PET agent but to provide a statement of relative safety with respect to radiation dosage to the critical organ for a given dosage which in this case was quoted as 25 mCi compared to the recommended dose range of 10-20 mCi.

Please note that the FDA draft labeling posted by the Agency for the future applicant's use in labeling included a range of 10-20 mCi. See example below:

The recommended dosages of Ammonia N 13 Injection, as an intravenous injection, are:

1. Rest Imaging Studies
 - a. A dose of 10-20 mCi is injected through a catheter inserted into a large vein.
 - b. After 3 minutes from the initial injection, resting data are acquired for 15-20 minutes.
2. Stress Imaging Studies
 - a. After 40 minutes from the initial injection (to allow for isotope decay), a pharmacologic stress-inducing drug may be administered in accordance with its approved labeling.

- b. After 8 minutes from the injection of the pharmacologic stress inducing drug, a second dose of Ammonia N 13 Injection 10-20 mCi may be injected. Images should be acquired for 15-20 minutes.

A review of the literature was performed by FDA (1999) addressing the safety and efficacy of N13 ammonia. The doses used in those studies that were included in the review are consistent with the originally proposed labeling shown above. The currently proposed labeling by the reviewing clinical team did not change the mCi dosing. See Section 9.4 below.

B. Image acquisition

The originally proposed labeling recommended an image acquisition time length of 15-20 (Demer, et al) minutes (see excerpt above). The length of time of image acquisition is shown to vary in the literature to support a range from 10-20 minutes which is reflected in the new labeling in section 9.4 below.

Seminars in Nuclear Medicine 2005; 35:17-36

The Journal of Nuclear Medicine 2007; 48(5):783-793

Journal of Nuclear Cardiology September 2003; 10(5):543-556

Circulation 1989; 80:1328-1337

8.2 Drug-Drug Interactions

There are no known drug-drug interactions.

8.3 Special Populations

No studies have been performed evaluating the dosing or use of the product with respect to demographics, coexisting states (e.g. hepatic, renal insufficiency) or pregnancy and lactation. Absorbed radiation dose per unit activity (rem/mCi) is available for ages 1, 5, 10 and 15 years old and can be found in the product labeling (Table 5).

8.4 Pediatrics

A pediatric waiver was requested in the appropriate section of the application. A pediatric waiver was granted to the applicant based upon the FR Notice of March 2000 and the medical review performed by the agency in 1999 which determined the product as being generally recognized as safe and effective in the pediatric population. Review of current literature supports the use of ammonia N13 in infants and children for the evaluation of myocardial perfusion.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

A literature review was performed by the applicant and by the FDA. Biosis, SciSearch on DialogSelect, PubMed, Embase, as well as Cambridge Scientific Abstracts systems were queried for adverse events regarding Ammonia N13. No citations were found. The databases were also searched for efficacy. The review focused on articles published subsequent to the FDA's original review. No definitive randomized controlled trials were found. The majority of the published literature reported single institutional experience that supported the original FDA findings of efficacy in adults and children.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety and efficacy of Ammonia N13 is sufficient to warrant approval.

9.2 Recommendation on Regulatory Action

The recommended regulatory action of this reviewer is Approval. A literature search performed by the Agency in 1999 and reevaluated for this submission as well as the FR notice of March 2000, the FDA's AERS database and more recent scientific literature, support the safety and efficacy of Ammonia N13 for myocardial imaging of the coronary arteries in patients with known or suspected coronary artery disease.

9.3 Recommendation on Postmarketing Actions

Not applicable.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

OSE consult results:

The reviewer agrees with the following recommendation. The statement _____ should be incorporated in the warnings on the label for the container closure system and the lead pig container. Additional stylistic changes were suggested for the labels of the container closure system and the lead pig container as well as the package insert.

DMETS consult results:

The reviewer agrees with the recommendations for changes in format and in wording and to requests to clarify certain statements in the package insert.

Recommended labeling changes by the clinical team:

A. Description of efficacy findings

The Agency published a Medical and Statistical Review of the literature written by DMIHP generally recognizing the safety and efficacy of Ammonia N13 as a PET agent for evaluating myocardial perfusion in patients with known or suspected coronary artery disease. Additionally, based on that review, the division prepared proposed labeling for the product. A notice was placed in the Federal Register (Vol 65, No. 48/March 10, 2000 Docket No. 00N-0553) announcing a request for applicants to submit an NDA for this product. The clinical reviewer evaluated FDA's Medical and Statistical Review of the literature and the proposed labeling. While the clinical reviewer agrees with the overall conclusion of the original FDA review regarding the safety and efficacy of the product, the reviewer believes that the interpretation of the data is not fully consistent with the data presented in the published article that was the principal basis of the finding of efficacy. The reviewer therefore recommends that the description of the study's results in the package insert be changed to be more descriptive in nature.

The primary article supporting the efficacy of Ammonia N13 as a PET imaging agent for myocardial perfusion in the original review is: Demer, et al. Assessment of coronary artery disease severity by PET: Comparison with quantitative Arteriography in 193 patients. *Circulation* 1989; 79: 825-835. In this article, the authors sought to "reevaluate the accuracy of positron perfusion imaging in assessment of coronary disease severity with scales covering the range of disease severity rather than binary classification, direct correlation rather than sensitivity-specificity analysis, and quantitative arteriographic flow reserve rather than percent diameter narrowing..." In short, the authors were exploring the relationship between PET and angiography (CA) in determining coronary perfusion as expressed by changes in stenosis flow reserve (SFR).

Study overview:

The initial patient population consisted of 209 patients who underwent both PET and coronary angiography. The results of the two tests were then interpreted and the results analyzed. PET studies of perfusion deficit were evaluated by two independent readers on a prespecified scale of 0-5: 0 is normal, 1 is possible, 2 is probable, 3 is mild, 4 is moderate, and 5 is severe. The average score of the two reads was used in the analysis. CA used a computer program to measure vessel borders. Stenosis flow reserve was defined and determined for each study. Analyses were then performed to determine the relation of PET defect severity to SFR via two methods: per artery and per patient.

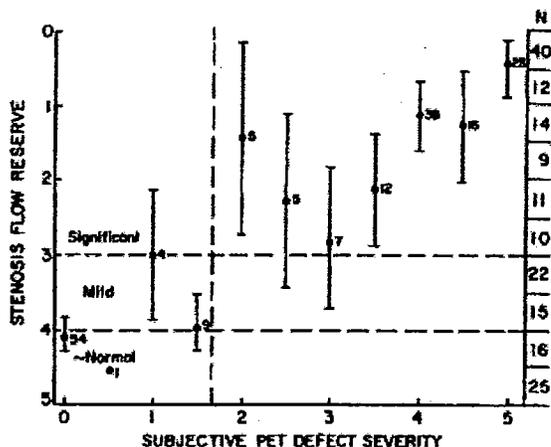
Study strengths:

1. All patients in the study had both imaging procedures performed.
2. Coronary angiography was recognized as the accepted standard of truth and used as a comparator.
3. The study included a large number of patients with suspected coronary disease.
4. Stenosis flow reserve was defined prospectively.
5. Acquisition and grading system for PET was prespecified.
6. The images were read independently by two readers. Variability in reader interpretation was evaluated and the procedure for resolution of discordant reads was defined.

Study weaknesses:

1. Used two isotopes for PET: Ammonia N13 (N=111) and Rubidium-82 (N= 82) and the data were pooled.
3. Missing data. The study enrolled 209 patients but only 174 patients were used in the analysis as plotted in figure 3 of the paper comparing PET defect severity to SFR. Patients were excluded based on imaging errors (N=16). Five patients had PET performed after acute MI after revascularization and were imputed as total occlusions in per patient analysis. Nineteen patients having acute revascularization were excluded from analysis.
4. The validation of quantitative arteriography to calculate SFR (linear parameter) as a comparator to PET is not provided.
5. The threshold for defining clinically important disease (PET) was not predefined. Instead, it was the aim of the study to show a correlation between SFR and the clinically important perfusion deficit value via PET. See figure 3 below.
6. The primary efficacy analysis was not prespecified.
7. In evaluating the data in figure 3 below, the PET score confidence intervals are wide and overlap (PET scores of 1-3) into more than one clinically defined arteriographic region.

Figure 3 part b (per patient evaluation) excerpted from Demer, et al.



FDA's Original Medical and Statistical review (1999):

While the Demer article was not designed to make S/S conclusions, FDA attempted to calculate sensitivity and specificity (S/S) from figure 3 despite incomplete data, pooling of isotopes, and making post-hoc assumptions on the threshold for clinically important CAD disease by PET evaluation. The conclusions of the original medical and statistical review are presented in the table below:

Coronary Angiography	PET Perfusion Defects ^(a,b,c)	
	None or Possible (N=68)	Probable to Severe (N=106)
None to Mild Stenosis	66	12
Significant Stenosis	2	94

a PET sensitivity 98% (95% confidence interval: 92.1 – 99.7%)

b PET specificity 85% (95% confidence interval: 74.7 – 91.7%)

c PET images are the pooled result of 111 patient image sets obtained with ammonia N 13 and 82 patient image sets obtained with Rubidium-82.

In this calculation, there were 12 false negatives and 2 false positives. Thus, further clinical work-up for patients involving angiography or other tests may be indicated.

The statement below the chart mislabels the categories of false negatives and false positives. The false positives are 12 and the false negatives are 2. The numbers placed in the various categories required arbitrary assumptions based on visual inspection of the graphical presentation of the confidence intervals. Therefore, the clinical reviewer believes that these calculations are not sufficiently conservative, and that there are insufficient data to

characterize the true sensitivity and specificity of the test agent. Citing point estimates in the label is potentially misleading.

Consequently, the reviewer recommends that the label be modified from a quantitative version to a version that is descriptive of the study and the statistical analysis of the Demer article.

The reviewer recommends:

1. Deletion of Table 4, its descriptive legend and the two sentences proposed below the table.
2. Replacement by the following:

In a descriptive, prospective, blinded image interpretation study² of adult patients with known or suspected coronary artery disease, myocardial perfusion deficits observed in PET images obtained with Ammonia N 13 (N=111) or Rubidium 82 (N=82) were _____

- B. The imaging time of the label has been updated to resolve an inconsistency in the originally proposed label and to reflect the current literature search. The 1999 proposed label suggested an optimal PET imaging time of 15-20 minutes in the General Clinical Pharmacology section. However, in the following paragraph, Pharmacodynamics, the suggested imaging time is 10 minutes. Again, in the originally proposed labeling Dosage and Administration section, the imaging time is listed as 15-20 minutes. In order to clarify this inconsistency in the label and to reflect the imaging acquisition protocols utilized in the current literature, the clinical reviewer recommends a change in the new label modifying the PET imaging time from 15-20 minutes to 10-20 minutes.

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/s/

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