CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-119/S-001

Name: Ammonia [N-13] Injection

Sponsor: The Feinstein Institute for Medical Research

Approval Date: January 5, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22119/S-001

SUPPLEMENT APPROVAL

The Feinstein Institute for Medical Research
North Shore/LIJ Health System
Cyclotron/Radiochemistry Facility
Attention: Thomas Chaly, Ph.D.
350 Community Drive
Manhasset, NY 11030

Dear Dr. Chaly:

Please refer to your Supplemental New Drug Application (sNDA) dated December 22, 2010, received December 23, 2010, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ammonia [N-13] Injection.

This "Prior Approval" supplemental new drug application provides for changes within Section 11 text and Table 3, as discussed during the teleconference of December 15 and outlined in the FDA Information Request of December 17, 2010.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

SUBMISSION REQUIREMENTS

All submissions regarding NDA 22119, should be submitted in *triplicate* hard copies (one original plus two desk copies) with a cover letter and Form FDA 356(h), along with **an electronic copy on CD-Rom (PDF)**, as with all submissions to the FDA CDER – Division of Medical Imaging Products, as follow:

Courier/Overnight/Postal
Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Attention: FDA Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Or solely electronic submission via Gateway / Global Submit Review (GSR) – See the following links for information:

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

If you have any questions regarding NDA 22119, contact Ms. Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager at (301) 796-1427 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ENCLOSURE: Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUY M NGUYEN
01/05/2011

RAFEL D RIEVES
01/05/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Ammonia N 13 Injection safely and effectively. See full prescribing information for Ammonia N 13 Injection.

Ammonia N 13 Injection for intravenous use
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------
Ammonia N 13 Injection is a radioactive diagnostic agent for Positron Emission Tomography (PET) 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 (1).

----------DOSAGE AND ADMINISTRATION----------
Rest Imaging Study (2.1):
- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10-20 mCi (0.368 – 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
- Start imaging 3 minutes after the injection and acquire images for a total of 10-20 minutes.

Stress Imaging Study (2.2):
- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N13 injection to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.
- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10-20 mCi (0.368 – 0.736 GBq) of Ammonia N 13 Injection as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
- Start imaging 3 minutes after the Ammonia N 13 Injection and acquire images for a total of 10-20 minutes.

Patient Preparation (2.3):
- To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, hydrate the patient before the procedure and encourage voiding as soon as each image acquisition is completed and as often as possible thereafter for at least one hour.

----------DOSAGE FORMS AND STRENGTHS----------
Glass vial containing 0.138-1.387 GBq (3.75-37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 8 mL volume) (3).

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
Ammonia N 13 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5).

----------ADVERSE REACTIONS----------
No adverse reactions have been reported for Ammonia N 13 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting system (6).

To report SUSPECTED ADVERSE REACTIONS, contact The Feinstein Institute for Medical Research at 516-562-1042 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- It is not known whether this drug is excreted in human milk. Alternatives to breastfeeding (e.g. using stored breast milk or infant formula) should be used for 2 hours (>10 half-lives of radioactive decay for N 13 isotope) after administration of Ammonia N 13 Injection (8.3).
- The safety and effectiveness of Ammonia N 13 Injection has been established in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION
Revised 01/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ammonia N 13 Injection is indicated for diagnostic 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.

2 DOSAGE AND ADMINISTRATION

2.1 Rest Imaging Study

- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10-20 mCi (0.368 – 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
- Start imaging 3 minutes after the injection and acquire images for a total of 10-20 minutes.

2.2 Stress Imaging Study

- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N 13 injection to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.
- Aseptically withdraw Ammonia N 13 Injection from its container and administer 10-20 mCi (0.368 – 0.736 GBq) of Ammonia N 13 Injection as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
- Start imaging 3 minutes after the Ammonia N 13 Injection and acquire images for a total of 10-20 minutes.

2.3 Patient Preparation

To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, ensure that the patient is well hydrated before the procedure and encourage voiding as soon as a study is completed and as often as possible thereafter for at least one hour.

2.4 Radiation Dosimetry

The converted radiation absorbed doses in rem/mCi are shown in Table 1. These estimates are calculated from the Task Group of Committee 2 of the International Commission on Radiation Protection.[1]

Table 1: N 13 Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups.

Organ	Age (years)				
	Adult	15	10	5	1
Adrenals	0.0085	0.0096	0.016	0.025	0.048
Bladder wall	0.030	0.037	0.056	0.089	0.17
Bone surfaces	0.0059	0.0070	0.011	0.019	0.037
Brain	0.016	0.016	0.017	0.019	0.027
Breast	0.0067	0.0067	0.010	0.017	0.033
Stomach wall	0.0063	0.0078	0.012	0.019	0.037
Small intestine	0.0067	0.0081	0.013	0.021	0.041
*ULI	0.0067	0.0078	0.013	0.021	0.037
**LLI	0.0070	0.0078	0.013	0.020	0.037
Heart	0.0078	0.0096	0.015	0.023	0.041
Kidneys	0.017	0.021	0.031	0.048	0.089
Liver	0.015	0.018	0.029	0.044	0.085
Lungs	0.0093	0.011	0.018	0.029	0.056
Ovaries	0.0063	0.0085	0.014	0.021	0.041
Pancreas	0.0070	0.0085	0.014	0.021	0.041
Red marrow	0.0063	0.0078	0.012	0.020	0.037
Spleen	0.0093	0.011	0.019	0.030	0.056
Testes	0.0067	0.0070	0.011	0.018	0.035
Thyroid	0.0063	0.0081	0.013	0.021	0.041
Uterus	0.0070	0.0089	0.014	0.023	0.041
Other tissues	0.0059	0.0070	0.011	0.018	0.035

* Upper large intestine, **Lower large intestine

2.5 Drug Handling

- Inspect Ammonia N 13 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer Ammonia N 13 Injection containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Wear waterproof gloves and effective shielding when handling Ammonia N 13 Injection.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Ammonia N 13 Injection. The contents of each vial are sterile and non-pyrogenic.
- Use appropriate safety measures, including shielding, consistent with proper patient management to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Before administration of Ammonia N 13 Injection, assay the dose in a properly calibrated dose calibrator.

3 DOSAGE FORMS AND STRENGTHS

Glass vial (20 mL) containing 0.138-1.387 GBq (3.75-37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 8 mL volume) that is suitable for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5 1 Radiation Risks

Ammonia N 13 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker *[see Dosage and Administration (2.4)]*.

6 ADVERSE REACTIONS

No adverse reactions have been reported for Ammonia N 13 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS

The possibility of interactions of Ammonia N 13 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Ammonia N 13 Injection. It is also 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 given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for radiation exposure to nursing infants from Ammonia N 13 Injection, use alternative infant nutrition sources (e.g. stored breast milk or infant formula) for 2 hours (>10 half-lives of radioactive decay for N 13 isotope) after administration of the drug or avoid use of the drug, taking into account the importance of the drug to the mother.

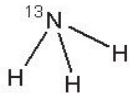
8.4 Pediatric Use

The safety and effectiveness of Ammonia N 13 Injection has been established in pediatric patients based on known metabolism of ammonia, radiation dosimetry in the pediatric population, and clinical studies in adults *[see Dosage and Administration (2.4)]*.

11 DESCRIPTION

11.1 Chemical Characteristics

Ammonia N 13 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, [^{13}N] ammonia, has the molecular formula of $^{13}NH_3$ with a molecular weight of 16.02, and has the following chemical structure:



Ammonia N 13 Injection is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains between 0.138 GBq to 1.387 GBq (3.75 mCi to 37.5mCi) of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 to 7.5. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.05-0.1 picomoles (8.47-16.94 picograms) of ammonia.

11.2 Physical Characteristics

Nitrogen N13 decays by emitting positron to Carbon C13 (stable) and has a physical half-life of 9.96 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

Table 2: Principal Radiation Emission Data for Nitrogen 13

Radiation/Emission	% Per Disintegration	Energy
Positron(β+)	100	1190 keV (Max.)
Gamma(±)*	200	511 keV

*Produced by positron annihilation

The specific gamma ray constant (point source air kerma coefficient) for nitrogen N13 is 5.9 R/hr/mCi (1.39 x 10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) of lead (Pb) for 511 keV photons is 4 mm. Selected coefficients of attenuation are listed in Table 3 as a function of lead shield thickness. For example, the use of 39 mm thickness of lead will attenuate the external radiation by a factor of about 1000.

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0.5
8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

Table 4 lists fractions remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Nitrogen N 13

Minutes	Fraction Remaining
0*	1.000
5	0.706
10	0.499
15	0.352
20	0.249
25	0.176
30	0.124

*Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ammonia N 13 Injection is a radiolabeled analog of ammonia that is distributed to all organs of the body after intravenous administration. It is extracted from the blood in the coronary capillaries into the myocardial cells where it is metabolized to glutamine N 13 and retained in the cells. The presence of ammonia N 13 and glutamine N 13 in the myocardium allows for PET imaging of the myocardium.

12.2 Pharmacodynamics

Following intravenous injection, ammonia N 13 enters the myocardium through the coronary arteries. The PET technique measures myocardial blood flow based on the assumption of a three-compartmental disposition of intravenous ammonia N 13 in the myocardium. In this model, the value of the rate constant, which represents the delivery of blood to myocardium, and the fraction of ammonia N 13 extracted into the myocardial cells, is a measure of myocardial blood flow. Optimal PET imaging of the myocardium is generally achieved between 10 to 20 minutes after administration.

12.3 Pharmacokinetics

Following intravenous injection, Ammonia N 13 Injection is cleared from the blood with a biologic half-life of about 2.84 minutes (effective half-life of about 2.21 minutes). In the myocardium, its biologic half-life has been estimated to be less than 2 minutes (effective half-life less than 1.67 minutes).

The mass dose of Ammonia N 13 Injection is very small as

compared to the normal range of ammonia in the blood (0.72-3.30 mg) in a healthy adult man *[see Description (11.1)]*.

Plasma protein binding of ammonia N 13 or its N 13 metabolites has not been studied.

Ammonia N 13 undergoes a five-enzyme step metabolism in the liver to yield urea N 13 (the main circulating metabolite). It is also metabolized to glutamine N 13 (the main metabolite in tissues) by glutamine synthesis in the skeletal muscles, liver, brain, myocardium, and other organs. Other metabolites of ammonia N 13 include small amounts of N 13 amino acid anions (acidic amino acids) in the forms of glutamate N 13 or aspartate N 13.

Ammonia N 13 is eliminated from the body by urinary excretion mainly as urea N 13.

The pharmacokinetics of Ammonia N 13 Injection have not been studied in renally impaired, hepatically impaired, or pediatric patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of Ammonia N 13 Injection. Genotoxicity assays and impairment of male and female fertility studies with Ammonia N 13 Injection have not been performed.

14 CLINICAL STUDIES

In a descriptive, prospective, blinded image interpretation study[2] of adult patients with known or suspected coronary artery disease, myocardial perfusion deficits in stress and rest PET images obtained with Ammonia N 13 (N=111) or Rubidium 82 (N=82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. The principal outcome of the study was the evaluation of PET defect severity relative to SFR.

PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects. Coronary angiograms were used to measure absolute and relative stenosis dimensions and to calculate stenosis flow reserve defined as the maximum value of flow at maximum coronary vasodilatation relative to rest flow under standardized hemodynamic conditions. SFR scores ranged from 0 (total occlusion) to 5 (normal).

With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

15 REFERENCES

[1]Annals of the ICRP. Publication 53. Radiation dose to patients from radiopharmaceuticals. New York: Pergamon Press, 1988.

[2]Demer, L.L.K.L.Gould, R.A.Goldstein, R.L.Kirkeeide, N.A.Mullani, R.W. Smalling, A.Nishikawa, and M.E.Merhige. Assessment of coronary artery disease severity by PET: Comparison with quantitative arteriography in 193 patients. Circulation 1989; 79: 825-35.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ammonia N 13 Injection is packaged in 20 mL multiple dose glass vial containing between 1 11 GBq to 11.1 GBq (30 mCi to 300 mCi) of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution in approximately 8 mL volume. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.05-0.1 picomoles (8.47-16.94 picograms) of Ammonia.

Storage

Store at 25 C (77 F); excursions permitted to 15-30 C (59-86 F). Use the solution within 30 minutes of the End of Synthesis (EOS) calibration.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration

Instruct patients to drink plenty of water or other fluids (as tolerated) in the 4 hours before their PET study.

17.2 Post-study Voiding

Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after the PET scan ends.

17.3 Post-study Breastfeeding Avoidance

Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for 2 hours after administration of Ammonia N 13 Injection.

Manufactured by: Feinstein Institute for Medical Research
North Shore/LIJ Health System
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030

Distributed by: Feinstein Institute for Medical Research
North Shore/LIJ Health System
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

LABELING REVIEWS

DIVISION OF MEDICAL IMAGING PRODUCTS

INTERNAL PM LABELING REVIEW

NDA: **22119**

DRUG NAME: **Ammonia [N-13] Injection**

SPONSOR: **Feinstein Institute**

SUBMISSION DATE: **December 22, 2010**

REVIEW DATE: **January 3, 2011**

Regarding the Sponsor's Prior Approval Labeling sNDA, EDR – submission dated December 22, 2010, the Sponsor has incorporated the following changes (below) into a revised labeling, as discussed during the teleconference of 12/15/10, and as outlined in the FDA Information Request dated 12/17/10:

The calculations for Table 3 were based upon information within the National Institute of Standards and Technology (NISTR 5632) Table 3 X-Ray Mass Attenuation Coefficients (http://www.nist.gov/pml/data/xraycoef/index.cfm).

1. Within section 11 text, revise the following:

FROM: "The specific gamma ray constant for nitrogen N13 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm."

TO: "The specific gamma ray constant for nitrogen N13 is 5.9 R/hr/mCi (1.39×10^{-6} Gy/hr/kBq) at 1 cm."

2. Within section 11 Table 3, revise the following:

FROM:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
4.1	0.5
8.3	0.25
13.2	0.1
26.4	0.01
52.8	0.001

TO:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0.5
8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

PM Labeling Review Completed By: T.Nguyen, DMIP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUY M NGUYEN
01/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

MEDICAL REVIEW

January 4th, 2011

Division of Medical Imaging and Hematology Products

Clinical Review of NDA Prior Approval Supplement

NDA:	22119
PAS Submission Date:	12/22/2010
Original Approval Date:	8/23/2007
Product:	Ammonia N 13 Injection
Sponsor:	Feinstein Institute Medical Research
Document Reviewer:	Phillip Davis, MD

I. Summary

This submission contains the sponsor's NDA Prior Approval Supplement (PAS) application, which is in response to DMIP's requested label changes, that were discussed with Dr. Thomas Chaly by teleconference 12/15/2010. The supplemental application proposes the following changes:

[The calculations for Table 3 were based upon information within the National Institute of Standards and Technology (NISTR 5632) Table 3 X-Ray Mass Attenuation Coefficients (http://www nist.gov/pml/data/xraycoef/index.cfm).]

1. Within section 11 text, revise the following:
FROM: "The specific gamma ray constant for nitrogen N13 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm."
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Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0.5
8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

II. Assessment and Plan

The sponsor's PAS contains all of DMIP's recommended revisions to the ammonia N13 label, and there are no other non-requested additions or changes.

The reviewer recommends approval of the sNDA application.

III. Additional Comments

For future reference, Dr. Louis Marzella recommended the following additional changes to the ammonia N13 label:

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Ammonia N 13 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker *[see Dosage and Administration (2.5)]*.

Comment – Section 5 proposed change is 2.4 changed to 2.5, seen in red.

Table 3: Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0 5
8	0 25
13	0 1
26	0 01
39	0 001
52	0 0001

Comment – Table 3 proposed changes are capitalizations, seen above in red.

12.3 Pharmacokinetics

Following intravenous injection, Ammonia N 13 Injection is cleared from the blood with a biologic half-life of about 2.84 minutes (effective half-life of about 2.21 minutes). In the myocardium, its biologic half-life has been estimated to be less than 2 minutes (effective half-life less than 1.67 minutes).

The mass dose of Ammonia N 13 Injection is very small as compared to the normal range of ammonia in the blood (0.72-3.30 mg/dL) in a healthy adult man *[see Description (11.1)]*.

Plasma protein binding of ammonia N 13 or its N 13 metabolites has not been studied.

Comment – Section 12.3 proposed change is insertion of dL, seen above in red.

15 REFERENCES

[2] L.L.Demer, K.L.Gould, R.A.Goldstein, R.L.Kirkeeide, N.A.Mullani, R.W. Smalling, A.Nishikawa, and M.E.Merhige. Assessment of coronary artery disease

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severity by positron emission tomography. Comparison with quantitative arteriography in 193 patients. Circulation 1989; 79: 825-35.

Deleted: PET:

Comment – Section 15 proposed changes are seen above in red.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ammonia N 13 Injection is packaged in 20 mL multiple dose glass vial containing between 1.11 GBq to 11.1 GBq (30 mCi to 300 mCi) of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution in approximately 8 mL volume. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.05-0.1 picomoles (8.47-16.94 picograms) of ammonia.

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Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Use the solution within 30 minutes of EOS calibration.

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Deleted:)

Comment – Section 16 proposed changes are seen above in red.

REVIEWED BY:

Phillip Davis, MD

Medical Officer

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/s/

PHILLIP B DAVIS
01/04/2011

LIBERO L MARZELLA
01/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-119/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

***CONFIDENTIAL**

U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

TELECONFERENCE MINUTES

NDAs: **21-870 [FDG] and 22-119 [Ammonia]**

SPONSOR: **Feinstein Institute**

DATE: **Wednesday, December 15, 2010 at 9:30 am**

DIAL-IN #: **(866) 750-2504**

SPONSOR PARTICIPANT
Thomas Chaly, P.h.D., FAIC, Radiochemist, Sponsor Representative
(b) (6), R.Ph., B.C.N.P., Radiochemist
(b) (6) Ph.D., Chemist

FDA PARTICIPANTS
Phillip Davis, M.D., Clinical Reviewer
Richard Fejka, R.Ph., Radiochemist
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager
Rafel Dwaine Rieves, M.D., Division Director
Orhan Suleiman, Ph.D., Radiation Physicist

AGENDA: To discuss FDG and Ammonia labeling revisions

During the FDA review of the labelings for approved positron emission tomography drugs – FDG and Ammonia, a few errors within certain computations were indentified. These errors were detected by FDA radiation physicist following repetitive recalculations under the package insert text constraints.

The Sponsor agreed to incorporate the revisions (below) and to submit to labeling supplements by January 7, 2011, (in PLR-SPL and MS Word Doc):

NDA 21-870 (FDG) Labeling

The calculations for Table 3 were based upon information within the National Institute of Standards and Technology (NISTR 5632) Table 3 X-Ray Mass Attenuation Coefficients (http://www.nist.gov/pml/data/xraycoef/index.cfm).

1. Within section 11 Table 3, revise the following:

FROM:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4.1	0.5
8.3	0.25
13.2	0.1
26.4	0.01
52.8	0.001

TO:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

NDA 22-119 (Ammonia) Labeling

The calculations for Table 3 were based upon information within the National Institute of Standards and Technology (NISTR 5632) Table 3 X-Ray Mass Attenuation Coefficients (http://www.nist.gov/pml/data/xraycoef/index.cfm).

1. Within section 11 text, revise the following:

FROM: "The specific gamma ray constant for nitrogen N13 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm."

TO: "The specific gamma ray constant for nitrogen N13 is 5.9 R/hr/mCi (1.39 x 10^{-6} Gy/hr/kBq) at 1 cm."

2. Within section 11 Table 3, revise the following:

FROM:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
4.1	0.5
8.3	0.25
13.2	0.1
26.4	0.01
52.8	0.001

TO:

Table 3: Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
4	0.5
8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

Minutes Recorded By: T.Nguyen, DMIP

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/s/

THUY M NGUYEN
12/21/2010

North Shore LIJ Institute for Medical Research
North Shore-Long Island Jewish Health System

350 Community Drive
Manhasset, New York 11030
Tel (516) 562-1042
Fax (516) 562-1041
tchaly@nshs.edu

THOMAS CHALY, Ph.D., FAIC

Chief, Radiochemistry
Cyclotron/Radiochemistry Facility

CDR

ORIGINAL

DATE: December 22, 2010

To: Dr. Rafel Dwaine Rieves M.D
Division Director
Division of Medical Imaging Products
Division of Drug Evaluation IV
FDA-Center for Drug Evaluation and Research
ATTN: Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

SD-18

From: Thomas Chaly Ph.D., FAIC
Associate Professor, NYU Medical College
Chief, Cyclotron/Radiochemistry
The Feinstein Institute for Medical Research
North Shore/LIJ Health System
350 Community Drive
Manhasset, New York 11030

Note: Approval - See Dawts 01/05/11

APPROVED NDA # 22-119

SUPPLEMENT # 22-119/S001

Name of the Drug: Ammonia N 13 Injection

Name of NDA Holder: The Feinstein Institute for Medical Research.

SUBJECT: NDA 22-119: Labeling Supplement Request for Amendments:

The Feinstein Institute for Medical Research is seeking permission from FDA to change the labeling of NDA 22-119.

Dear Dr. Rieves,

Based on the teleconference with you and the FDA panel on December 15, 2010, I have revised the labeling for Ammonia N 13 Injection (NDA 22-119). I completely agree with the revisions suggested by the FDA team and I have incorporated all the suggestions in this supplement. I am looking forward to the approval of this supplement in the near

future. I would appreciate it, if you could provide me with the original document of the approved label, as soon as it is available.

I take this opportunity to thank you and the FDA team for all the constructive suggestions to prepare this labeling supplement. I like to express my sincere thanks to Dr. Thuy Nguyen for all the help and support.

Sincerely

Thomas Chaly Ph.D

The following documents are included with this submission.

1. This letter in triplicate
2. FDA Form 356h in triplicate
3. The new Label in triplicate
4. Electronic Version of the Labeling Supplement- One CD

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22119/S-001

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

The Feinstein Institute for Medical Research
North Shore/LIJ Health System
Cyclotron/Radiochemistry Facility
Attention: Thomas Chaly, Ph.D.
350 Community Drive
Manhasset, NY 11030

Dear Dr. Chaly:

We have received your Supplemental New Drug Application (sNDA) dated December 22, 2010, submitted pursuant to section 505(b)(2), of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22119

SUPPLEMENT NUMBER: S-001

PRODUCT NAME: Ammonia [N- 13] Injection

DATE OF SUBMISSION: December 22, 2010

DATE OF RECEIPT: December 23, 2010

This supplemental application proposes the following changes:

The calculations for Table 3 were based upon information within the National Institute of Standards and Technology (NISTR 5632) Table 3 X-Ray Mass Attenuation Coefficients (http://www.nist.gov/pml/data/xraycoef/index.cfm).

1. Within section 11 text, revise the following:

FROM: "The specific gamma ray constant for nitrogen N13 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm."

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8	0.25
13	0.1
26	0.01
39	0.001
52	0.0001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the Goal Date will be June 23, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Reference NDA 22119, in all communications/submissions with the FDA. Each submission to this NDA must be submitted in *triplicate* hard copies (one original plus two desk copies) with a cover letter and Form FDA 356(h), along with **an electronic copy on CD-Rom (PDF)**, as with all submissions to the FDA CDER – Division of Medical Imaging Products, as follow:

Courier\Overnight\Postal
Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Attention: FDA Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Or solely electronic submission via Gateway \ Global Submit Review (GSR) – See the following links for information:

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

If you have questions regarding NDA 22119, please contact me at (301) 796-1427 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thuy M. Nguyen, M.P.H.
Senior Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

THUY M NGUYEN
01/04/2011