

**AMMONIA N 13 - ammonia n-13 injection**  
**The Johns Hopkins University**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Ammonia N 13 Injection USP safely and effectively.

See full prescribing information for Ammonia N 13 Injection USP.

**Ammonia N 13 Injection USP for intravenous use**

**Initial U.S. Approval: 2007**

----- **INDICATIONS AND USAGE** -----

Ammonia N 13 Injection USP 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 mCi-20 mCi (0.368 GBq – 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 mCi-20 mCi (0.368 GBq – 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 (20 mL) containing 0.138 GBq/mL-1.387 GBq/mL (3.75 mCi/mL-37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 13 mL volume) that is suitable for intravenous administration.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 Johns Hopkins University PET Facility at 1-410-955-2916 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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: 8/2014**

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

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

Ammonia N 13 Injection USP 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 mCi-20 mCi (0.368 GBq – 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 mCi-20 mCi (0.368 GBq – 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.<sup>1</sup>

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

| Organ           | Adult  | 15 - year old | 10 - year old | 5 - year old | 1 - year old |
|-----------------|--------|---------------|---------------|--------------|--------------|
| 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 GBq/mL-1.387 GBq/mL (3.75 mCi/mL-37.5 mCi/mL) of Ammonia N 13 Injection in aqueous 0.9 % sodium chloride solution (approximately 13 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.

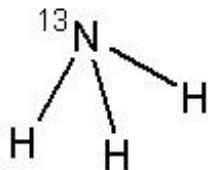
### 8.4 Pediatric Use

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 USP is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, [<sup>13</sup>N] ammonia, has the molecular formula of <sup>13</sup>NH<sub>3</sub> 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 [<sup>13</sup>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 mCi-20 mCi) is associated with a theoretical mass dose of 0.5 - 1.0 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( $\beta^+$ ) | 100                  | 1190 keV (Max.) |
| Gamma( $\pm$ )*       | 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 ( $1.39 \times 10^{-6}$  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<sup>2</sup> 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 USP is packaged in 20 mL multiple dose glass vial containing between 1.11 GBq to 11.1 GBq (30 mCi to 300 mCi) of [<sup>13</sup>N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution (approximately 13 mL volume). The recommended dose of radioactivity (10 mCi-20 mCi) is associated with a theoretical mass dose of 0.5-1.0 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 and Distributed by:  
Johns Hopkins University PET Facility  
3400 N. Charles Street  
Baltimore, MD 21218

## **Drug Product Label**



|                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                       |                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Ammonia N 13 Injection USP</b><br>3.75 mCi – 37.5 mCi/mL at EOS*<br>Diagnostic - For Intravenous Use Only<br>Sterile, Non-pyrogenic Expires 1 hour after EOS<br>Batch #: [ <sup>13</sup> N]NH <sub>3</sub> - _____<br>EOS Date: _____ EOS Time: _____<br>Activity @ EOS: _____ mCi<br>Concentration: _____ mCi/mL<br>Volume: _____ mL<br>Exp. Date: _____ Exp. Time: _____<br>*EOS = End of Synthesis | <b>NDC# 40089-113-20</b><br>Each mL contains 0.138 GBq to 1.387 GBq (3.75 mCi to 37.5 mCi) of no carrier added Ammonia N13 at EOS in 0.9% Sodium Chloride Injection                                                                                                                                                     | <b>20 mL Multiple-Dose Vial</b><br>Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Store upright in shielded container. Aseptically withdraw and handle doses. |  |
|                                                                                                                                                                                                                                                                                                                                                                                                          | Do not use if cloudy or if it contains particulate matter.<br>Calculate correct dosage from date and time of calibration (EOS).<br><b>CAUTION: RADIOACTIVE MATERIAL<br/> RX ONLY</b><br>Manufactured by The Johns Hopkins University PET Facility,<br>Baltimore, Maryland 21287<br><sup>13</sup> N Half-life = 9.96 min |                                                                                                                                                                                                                       |                                                                                    |

## AMMONIA N 13

nh3n13 injection

### Product Information

|                                |                         |                           |               |
|--------------------------------|-------------------------|---------------------------|---------------|
| <b>Product Type</b>            | HUMAN PRESCRIPTION DRUG | <b>Item Code (Source)</b> | NDC:40089-113 |
| <b>Route of Administration</b> | INTRAVENOUS             | <b>DEA Schedule</b>       |               |

### Active Ingredient/Active Moiety

| Ingredient Name                                                  | Basis of Strength | Strength         |
|------------------------------------------------------------------|-------------------|------------------|
| AMMONIA N-13 (UNII: 9OQO0E343Z) (AMMONIA N-13 - UNII:9OQO0E343Z) | AMMONIA N-13      | 37.5 mCi in 1 mL |

### Inactive Ingredients

| Ingredient Name                    | Strength     |
|------------------------------------|--------------|
| Sodium chloride (UNII: 451W47IQ8X) | 9 mg in 1 mL |

### Packaging

| # | Item Code        | Package Description    | Marketing Start Date | Marketing End Date |
|---|------------------|------------------------|----------------------|--------------------|
| 1 | NDC:40089-113-20 | 20 mL in 1 VIAL, GLASS |                      |                    |

### Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|------------------------------------------|----------------------|--------------------|
| ANDA               | ANDA204514                               | 03/21/2012           |                    |

**Labeler** - The Johns Hopkins University (001910777)

**Registrant** - The Johns Hopkins University (001910777)

### Establishment

| Name | Address | ID/FEI | Business Operations |
|------|---------|--------|---------------------|
|------|---------|--------|---------------------|

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The Johns Hopkins University