**Ammonia N 13 - ammonia n-13 injection**
NCM USA Bronx LLC

**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: 2005

**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, USP 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, USP from its container and administer 10-20 mCi (0.368 – 0.736 GBq) of Ammonia N 13 Injection, USP 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, USP 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 0.139-9.620 GBq (3.75-260 mCi/mL) of Ammonia N 13 Injection, USP in aqueous 0.9 % sodium chloride solution (3).

**CONTRAINDICATIONS**
None(4)

**WARNINGS AND PRECAUTIONS**
Ammonia N 13 Injection, USP 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, USP 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 NCM-USA Bronx at 212-719-2322 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, USP. (8.3).
- The safety and effectiveness of Ammonia N 13 Injection, USP has been established in pediatric patients(8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2016
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, USP 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, USP to allow sufficient isotope decay.

- Administer a pharmacologic stress-inducing drug in accordance with its labeling.

- Aseptically withdraw Ammonia N 13 Injection, USP 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, USP 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          |
2.5 Drug Handling

- Inspect Ammonia N 13 Injection, USP visually for particulate matter and discoloration before administration, whenever solution and container permit.

- Do not administer Ammonia N 13 Injection, USP 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, USP.

- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Ammonia N 13 Injection, USP. 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, USP, assay the dose in a properly calibrated dose calibrator.

3 DOSAGE FORMS AND STRENGTHS

Glass vial 30 mL containing 0.139-9.620 GBq/mL (3.75-260 mCi/mL) of Ammonia N 13 Injection, USP in aqueous 0.9 % sodium chloride solution that is suitable for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Ammonia N 13 Injection, USP 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, USP 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, USP 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, USP. It is also not known whether Ammonia N 13 Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ammonia N 13 Injection, USP 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, USP, 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, USP 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, [\(^{13}\text{N}\)] ammonia, has the molecular formula of \(^{13}\text{NH}_3\) with a molecular weight of 16.02, and has the following chemical structure:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{H}
\end{array}
\]

Ammonia N 13 Injection, USP is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains between 0.139 GBq to 9.620 GBq (3.75 mCi to 260 mCi) of [\(^{13}\text{N}\)] 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 0.5-1 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>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron(β+)</td>
<td>100</td>
<td>1190 keV (Max.)</td>
</tr>
<tr>
<td>Gamma(±)*</td>
<td>200</td>
<td>511 keV</td>
</tr>
</tbody>
</table>

* Produced by positron annihilation

The specific gamma ray constant for nitrogen N13 is 6.0 R/hr/mCi (1.35 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>
<thead>
<tr>
<th>Shield Thickness (Pb) mm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
</tr>
<tr>
<td>13</td>
<td>0.1</td>
</tr>
<tr>
<td>26</td>
<td>0.01</td>
</tr>
<tr>
<td>39</td>
<td>0.001</td>
</tr>
<tr>
<td>52</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Minutes</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1.000</td>
</tr>
<tr>
<td>5</td>
<td>0.706</td>
</tr>
<tr>
<td>10</td>
<td>0.499</td>
</tr>
<tr>
<td>15</td>
<td>0.352</td>
</tr>
<tr>
<td>20</td>
<td>0.249</td>
</tr>
<tr>
<td>25</td>
<td>0.176</td>
</tr>
<tr>
<td>30</td>
<td>0.124</td>
</tr>
</tbody>
</table>

* Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ammonia N 13 Injection, USP 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, USP 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, USP 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, USP 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, USP. Genotoxicity assays and impairment of male and female fertility studies with Ammonia N\(_{13}\) Injection, USP 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

16 HOW SUPPLIED
Ammonia N 13 Injection, USP is packaged in 30 mL multiple dose glass vial containing between 0.139 - 9.620 GBq/mL (3.75 - 260 mCi/mL) of $[^{13}\text{N}]$ ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution. The recommended dose of radioactivity (10-20 mCi, 370-740 MBq) is associated with a theoretical mass dose of 0.5-1 picomoles (8.47-16.94 picograms) of Ammonia.
NDC Code: 24445-643-30
This radiopharmaceutical is licensed by the State of New York, Department Of Health, Bureau of Environmental Radiation Protection, for distribution to persons licensed pursuant to New York's Regulatory Code for Radioactive material specified in Chapter 1-Part 16 of the State Sanitary Code, as appropriate, or under equivalent licenses of an Agreement State or Licensing State.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Use the solution within 60 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, USP.

Expiration Date and Time
The expiration date and time are provided on the container label.

Caution: Rx ONLY
Manufactured by: NCM-USA Bronx LLC, Bronx, NY 10454
Distributed by: NCM-USA Bronx LLC, Bronx, NY 10454

Drug Product Label
A. Label for the lead storage container

**NDC: 24445-643-30**

**Ammonia N13 Injection, USP**

3.75 mCi/mL to 260 mCi/mL at End of Synthesis (EOS)

Activity @ EOS: ______ mCi Volume: ______ mL

Concentration: ____________________ mCi/mL

Batch #: ___________ Sub-Batch#: ____

EOS Date: _______ EOS Time: _______

EXP. Date/Time: ________/______ (_____ m after EOS)

Diagnostic – For Intravenous Use Only
Sterile, Non-pyrogenic

Contains:
139 MBq to 9620 MBq (3.75 mCi/mL to 260 mCi/mL) of no-carrier added Ammonia N13 at EOS in 0.9% Sodium Chloride Injection

Store at 25°C (77°F)


**CAUTION: RADIOACTIVE MATERIAL**

RX ONLY 13N Half-life: 9.96 min

Manufactured by NCM USA, LLC. Bronx, NY 10454

B. Label for the Final Product Vial (FPV)

**NDC: 24445-643-30 Multiple-Dose Vial, Sterile, Non-pyrogenic**

Ammonia N13 Injection, USP (3.75-260 mCi/ml (@ EOS*))

Calibration Date _________________

Batch # _______________ Sub Batch# __________

Manufactured by:
NCM USA, LLC
390 Concord Avenue
Bronx, NY 10454

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**AMMONIA N 13   N 13**

ammonia n-13 injection

**Product Information**

**Product Type**
HUMAN PRESCRIPTION DRUG

**Item Code (Source)**
NDC:24445-643

**Route of Administration**
INTRAVENOUS

**Active Ingredient/Active Moiety**

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<th>Basis of Strength</th>
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<tr>
<td>AMMONIA N-13 (UNII: 9OQO0E343Z) (AMMONIA N-13 - UNII:9OQO0E343Z)</td>
<td>AMMONIA N-13</td>
<td>260 mCi in 1 mL</td>
</tr>
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**Inactive Ingredients**

<table>
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<tr>
<th>Ingredient Name</th>
<th>Strength</th>
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<tbody>
<tr>
<td>Sodium Chloride (UNII: 451W47IQ8X)</td>
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**Packaging**

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Labeler - NCM USA Bronx LLC (969267710)

Establishment

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