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Positron Emission Tomography Cardiac Reimbursement

Cardiac PET for Perfusion of the Heart

The information below is taken from Medicare National Coverage Determinations Manual[1]:

- Positron emission tomography (PET) scans performed at rest or with pharmacological stress used for non-invasive imaging of the perfusion of the heart for the diagnosis and management of patients with known or suspected coronary artery disease using the FDA-approved radiopharmaceutical ammonia N 13 injection* ($^{13}N\ NH_3$) are covered, provided the requirements below are met:

- The PET scan, whether at rest alone, or rest with stress, is performed in place of, but not in addition to, a single photon emission computed tomography (SPECT); or

- The PET scan, whether at rest alone or rest with stress, is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the patient. (For purposes of this requirement, an inconclusive test is a test where the results are equivocal, technically uninterpretable, or discordant with a patient's other clinical data and must be documented in the beneficiary's file.)[1]

Medicare covers PET exams to assess myocardial perfusion in place of, but not in addition to, SPECT or following an inconclusive SPECT.[2]

Current Procedural Terminology (CPT) Codes

78491	– Myocardial imaging, PET, perfusion; single study at rest or stress
78492	– Myocardial imaging, PET, perfusion; multiple studies at rest or stress
A9555	– 82Rubidium, diagnostic, per study dose, up to 60 millicuries
A9526	– ^{13}N Ammonia, diagnostic, per study dose, up to 40 millicuries

***AMMONIA N 13 INJECTION for Intravenous Use**

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.

IMPORTANT SAFETY INFORMATION

- **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.

- **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.

Siemens' PETNET Solutions is a manufacturer of Ammonia N 13 Injection. Indication and important safety information as approved by the US Food and Drug Administration can be found at the links below for ^{13}N Ammonia, adult dose 8-12 mCi, administered by intravenous injection.

Full Prescribing Information for Ammonia N 13 Injection can be found on pages 18-24.

Ammonia N 13 Injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

[1] Medicare National Coverage Determinations Manual Chapter 1, Part 4 (Section 220.6.1 PET for Perfusion of the Heart (Various Effective Dates) (Rev. 120; Issued: 05-06-10; Effective Date: 04-03-09; Implementation Date: 10-30-09) http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/ncd103c1_part4.pdf

[2] Medicare Claims Processing Manual revised July 2007, Chapter 13, Section 60.3.2 Tracer Codes Required for PET Scans. (Rev. 2096, Issued: 11-19-10, Effective: 02-26-10, Implementation: 02-22-11) can be found at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c13.pdf

Cardiac PET for Viability of the Heart

The identification of cardiac muscle segments with decreased blood flow at stress and rest and decreased resting muscle contractility, but with intact cellular integrity, a condition termed as hibernating myocardium is important in selecting candidates with compromised ventricular function to determine appropriateness for revascularization. Diagnostic tests such as ^{18}F FDG PET** distinguish between dysfunctional but viable myocardial tissue and scar tissue in order to affect management decisions in patients with ischemic cardiomyopathy and left ventricular dysfunction.

Medicare covers ^{18}F FDG PET for the determination of myocardial viability as a primary or initial diagnostic study prior to revascularization or following an inconclusive SPECT.

Limitations: In the event a patient receives a SPECT test with inconclusive results, a PET scan may be covered. However, if a patient receives an ^{18}F FDG PET study with inconclusive results, a follow-up SPECT test is not covered.

Documentation that these conditions are met should be maintained by the referring physician in the beneficiary's medical record, as is normal business practice.[1]

Current Procedural Terminology (CPT) Codes

78459 – Myocardial imaging, PET, metabolic evaluation
A9552 – ^{18}F FDG, per dose

****Fludeoxyglucose F 18 Injection for Intravenous Use**

INDICATIONS AND USAGE

Fludeoxyglucose F 18 injection (^{18}F FDG) is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with existing cancer diagnoses
- **Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging
- **Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures

IMPORTANT SAFETY INFORMATION

- **Radiation Risk**
  Radiation-emitting products, including ^{18}F FDG, may increase the risk for cancer, especially in pediatric patients.
  Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.
- **Blood Glucose Abnormalities**
  In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to ^{18}F FDG.
- **Adverse Reactions**
  Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.
- **Dosage Forms and Strengths**
  Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

Full prescribing information for Fludeoxyglucose F 18 Injection can be found on pages 15-17.

Fludeoxyglucose F 18 injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

Indications for PET for diagnostic purposes[1]

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
As the initial test for symptomatic patients at increased risk for CAD, defined as having risk for hard cardiac events (cardiovascular death or non-fatal myocardial infarction)	413.9, 414.8–414.9, 786.05–786.09, 786.50–786.59	AUC indication(s) 3 and 4

Diagnostic literature supporting cardiac PET study

[1] Beanlands R, Dick A, Chow B, et al. CCS; CAR; CANM; CNCS; and CanSCMR Position Statement on Advanced Noninvasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi- Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease. *Can J Cardiol.* 2007 Feb;23(2):107-19

[2] Di Carli, MF, Dorbala, S, Meserve, J, El Fakhri, G, Sitek, A, & Moore, SC. Clinical Myocardial Perfusion PET/CT. *J Nucl Med.* 2007;48(5):783-793

[3] Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc- 99m sestamibi SPECT. J Nucl Cardiol. 2006;13:24-33

[4] Sampson UK, Limaye A, Dorbala S, et al. Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography (PET-CT) in the detection of coronary artery disease. *J Am Coll Cardiol.* 2007;49:1052-1058

[5] Nandalur KR, Dwamena BA, Choudhri AF, Nandalur SR, Reddy P, Carlos RC. Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a metaanalysis. *Acad Radiol* 2008;15:444-451

Patients who have nonatherosclerotic CAD, including coronary anomalies	446.1, 446.7, 746.8–746.89	AUC does not address this, but it is supported by ASNC guidelines PET myocardial perfusion and Glucose metabolism imaging Standardized reporting of radionuclide myocardial perfusion and function

Diagnostic literature supporting cardiac PET study

[1] Brunken RC, Perloff JK, Czernin J, Campisi R, Purcell S, Miner PD, Child JS, Schelbert HR. Myocardial perfusion reserve in adults with cyanotic congenital heart disease. *Am J Physiol Heart Circ Physiol.* 2005 Nov;289(5):H1798-806. Epub 2005 Jul 8. PubMed PMID: 16006539

[2] Furuyama H, Odagawa Y, Katoh C, Iwado Y, Yoshinaga K, Ito Y, Noriyasu K, Mabuchi M, Kuge Y, Kobayashi K, Tamaki N. Assessment of coronary function in children with a history of Kawasaki disease using (15)O-water positron emission tomography. *Circulation.* 2002 Jun 18;105(24):2878- 84. PubMed PMID: 12070117

[3] Singh TP, Humes RA, Muzik O, Kottamasu S, Karpawich PP, Di Carli MF. Myocardial flow reserve in patients with a systemic right ventricle after atrial switch repair. J Am Coll Cardiol. 2001 Jun 15;37(8):2120-5. PubMed PMID: 11419897 Hauser M, Bengel FM, Kühn A, Sauer U, Zylla S, Braun SL, Nekolla SG, Oberhoffer R, Lange R, Schwaiger M, Hess J. Myocardial blood flow and flow reserve after coronary reimplantation in patients after arterial Switch and Ross operation. *Circulation.* 2001 Apr 10;103(14):1875-80. PubMed PMID: 11294806

[4] Bengel FM, Hauser M, Duvernoy CS, Kuehn A, Ziegler SI, Stollfuss JC, Beckmann M, Sauer U, Muzik O, Schwaiger M, Hess J. Myocardial blood flow and coronary flow reserve late after anatomical correction of transposition of the great arteries. *J Am Coll Cardiol.* 1998 Dec;32(7):1955-61. PubMed PMID: 9857878

As the initial test in patients with diabetes mellitus, with or without symptoms of suspected angina or coronary disease	780.02, 786.05–09, 786.50–59, 413.9	AUC indication(s) 3, 4, and 5

Diagnostic literature supporting cardiac PET study

[1] Di Carli, MF, Dorbala, S, Meserve, J, El Fakhri, G, Sitek, A, & Moore, SC. Clinical Myocardial Perfusion PET/CT. *J Nucl Med.* 2007;48(5):783-793

[2] Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECGgated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol.* 2006;13:24-33

[3] Sampson UK, Limaye A, Dorbala S, et al. Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography (PET-CT) in the detection of coronary artery disease. *J Am Coll Cardiol.* 2007;49:1052-1058

[4] Grover-McKay M, Ratib O, Schwaiger M, et al. Detection of coronary artery disease with positron emission tomography and rubidium 82. *Am Heart J.*1992;123:646-652

[5] Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission tomography: comparison with quantitative arteriography in 193 patients. *Circulation.* 1989;79:825-835

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with suspected coronary disease in whom an abnormal baseline ECG interferes with interpretation of exercise-induced ST segment deviations	426.1, 426.2, 426.10 –426.93	AUC indication(s) 2, 4, 14, and 15

Diagnostic literature supporting cardiac PET study

[1] Beanlands R, Dick A, Chow B, et al. CCS; CAR; CANM; CNCS; and CanSCMR Position Statement on Advanced Noninvasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease. *Can J Cardiol.* 2007 Feb;23(2):107-19

[2] Effects of left bundle branch block on myocardial FDG PET in patients without significant coronary artery stenoses. http:// www.ncbi.nlm.nih.gov/pubmed/10855620[Zanco P, Desideri A, Mobilia G, Cargnel S, Milan E, Celegon L, Buchberger R, Ferlin G. *J Nucl Med.* 2000 Jun;41(6):973-7

[3] Myocardial perfusion, glucose utilization and oxidative metabolism in a patient with left bundle branch block, prior myocardial infarction and diabetes. http://www. ncbi.nlm.nih.gov/pubmed/9476932[Zanco P, Chierichetti F, Fini A, Cargnel S, Ferlin G. *J Nucl Med.* 1998 Feb;39(2):261-3

[4] ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging— executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). http://www.ncbi.nlm.nih.gov/ pubmed/14522503[Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology. *J Am Coll Cardiol.* 2003 Oct 1;42(7):1318-33

Coronary flow reserve evaluation		AUC does not address this, but it is supported by ASNC guidelines PET myocardial perfusion and glucose metabolism Imaging Standardized reporting of radionuclide myocardial perfusion and function

Diagnostic literature supporting cardiac PET study

[1] Camici, P. G., Gistri, R., Lorenzoni, R., Sorace, O., Michelassi, C., Bongiorni, M. G., et al. (1992). Coronary reserve and exercise ECG in patients with chest pain and normal coronary angiograms. *Circulation,* 86(1), 179-186

[2] Geltman EM, Henes CG, Senneff MJ, Sobel BE, Bergmann SR. Increased myocardial perfusion at rest and diminished perfusion reserve in patients with angina and angiographically normal coronary arteries. *J Am Coll Cardiol.* 1990 Sep;16(3):586-95

[3] Masuda, D., Nohara, R., Tamaki, N., Hosokawa, R., Inada, H., Hikai, T., et al. (2000). Evaluation of coronary blood flow reserve by ^{13}N-NH_3 positron emission computed tomography (PET) with dipyridamole in the treatment of hypertension with the ACE inhibitor (cilazapril). *Annals of Nuclear Medicine*, 14(5), 353-360

[4] Ziadi MC, Dekemp RA, Williams K, Guo A, Renaud JM, Chow BJ, Klein R, Ruddy TD, Aung M, Garrard L, Beanlands RS. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? *J Nucl Cardiol.* 2012 Mar 14.

Patients with an abnormal exercise stress ECG without angina symptoms, to further determine whether CAD is present. For example: Patients with an intermediate to high Duke treadmill score	794.30, 794.31	AUC indication(s) 29, 38, and 39

Diagnostic literature supporting cardiac PET study

[1] Dayanikli F, Grambow D, Muzik O, Mosca L, Rubenfire M, Schwaiger M. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation* 1994;90:808-817

All patients who are asymptomatic, or have low to intermediate probability of CAD, but have an occupation that places other individuals at risk if they suffer a coronary event	414.0, 411, V71.7	AUC does not address this clinical scenario, but testing is supported by ACC/ASNC/AHA Guidelines. The role of radionuclide MPI for asymptomatic individuals

Diagnostic literature supporting cardiac PET study

[1] Blair RE. Coronary Artery Disease in a Young USAF Pilot: Screening for Premature Atherosclerosis. *Military Medicine* 2010;175(9):688-690

[2] Houston S, Mitchell S, Evans S. Application of a Cardiovascular Disease Risk Prediction Model Among Commercial Pilots. Aviat Space Environ Med 2010;81:768-773

[3] 2003 ACC/ASNC/AHA Guidelines for Clinical Use of Radionuclide Imaging. *J Am Coll Card* 2003;42:1318

[4] Hendel RC, Abbott BG, Bateman TM, Blankstein R, Calnon DA, et al. ASNC Information Statement. The role of radionuclide myocardial perfusion imaging for asymptomatic individuals. *J Nucl Cardiol* 2011;18(1):3-15

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients who have suspected CAD and who have a condition which would prevent them from achieving a diagnostically adequate level of cardiac stimulation (85% predicted maximum heart rate) on standard exercise ECG stress testing	719.7, 781.2, 443.9, 440.21, 278.00, 278.01, along with the applicable chest pain codes 786.50–786.59	AUC indication(s) 2 and 4

Diagnostic literature supporting cardiac PET study

[1] Buckley, O., Doyle, L., Padera, R., Lakdawala, N., Dorbala, S., Di Carli, M., et al. Cardiomyopathy of uncertain etiology: Complementary role of multimodality imaging with cardiac MRI and ^{18}FDG PET. *Journal of Nuclear Cardiology.* 2010;17(2):328-332

[2] Shikama, N., Himi, T., Yoshida, K., Nakao, M., Fujiwara, M., Tamura, T., et al. (1999). Prognostic utility of myocardial blood flow assessed by N-13 ammonia positron emission

[3] Tomography in patients with idiopathic dilated cardiomyopathy. *American Journal of Cardiology,* 84(4), 434-439

[4] Perrone-Filardi, P., Bacharach, S.L., Dilsizian, V., Panza, J.A., Maura, S., & Bonow, R.O. (1993). Regional systolic function, myocardial blood flow and glucose update at rest in hypertrophic cardiomyopathy. *American Journal of Cardiology*, 72(2), 199-204

[5] Hendel RC, Abbott BG, Bateman TM, Blankstein R, Calnon DA, et al. ASNC Information Statement. The role of radionuclide myocardial perfusion imaging for asymptomatic individuals. *J Nucl Cardiol* 2011;18(1):3-15

Patients with hypertrophic cardiomyopathy in whom PET is performed to define microvascular disease or to evaluate prognosis in patients with hypertrophic cardiomyopathy	425.10, 425.0–425.9, 413.9, 786.5, 411, 786.05–786.09, 780.02	AUC does not address this,but it is supported by ASNC guidelines PET myocardial perfusion and glucose Metabolism imaging Standardized reporting of radionuclide Myocardial perfusion and function

Diagnostic literature supporting cardiac PET study

[1] Timmer, S. A., Germans, T., Gotte, M. J., Russel, I. K.,Lubberink, M., Ten Berg, J. M., et al. (2011). Relation of coronary microvascular dysfunction in hypertrophic cardiomyopathy to contractile dysfunction independent from myocardial injury. *American Journal of Cardiology,* 107(10), 1522-1528

[2] Camici, P., Chiriatti, G., Lorenzoni, R., Bellina, R. C., Gistri, R., Italiani, G., et al. (1991). Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: A study with nitrogen-13 ammonia and positron emission tomography. *Journal of the American College of Cardiology*, 17(4), 879-886

[3] Cecchi, F., Olivotto, I., Gistri, R., Lorenzoni, R., Chiriatti, G., & Camici, P. G. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *New England Journal of Medicine*. 2003;349(11):1027-1035

Patients with valvular heart disease in whom PET is performed to differentiate coronary vs. non-coronary causes of chest discomfort	395.2–395.90	

Diagnostic literature supporting cardiac PET study

[1] Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, Hertenstein GK, Moutry KL, Reid K, Cullom SJ. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT

[2] Nandalur KR, Dwamena BA, Choudhri AF, Nandalur SR, Reddy P, Carlos RC. Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a metaanalysis. *Acad Radiol* 2008;15:444-451

Patients with cardiac transplantation in whom PET is performed to evaluate the presence of transplant vasculopathy	996.83, V42.1	AUC indication(s) 15

Diagnostic literature supporting cardiac PET study

[1] Wu YW, Chin YH, Wang SS et al. PET Assessment of myocardial perfusion reserve inversely correlates with intravascular ultrasound findings in angiographically normal cardiac transplant recipients. *J Nucl Med* 2010;51:906-912

[2] Preumont N, Beerkenboom G, Vachery JL, et al. Early alterations in myocardial blood flow reserve in heart transplant recipients with angiographically normal coronary arteries. *J Heart Lung Transplantation* 2000;19:53-544

[3] Allen-Auerbach M, Schoder H, Johnson J, et al. Relationship between coronary function by positron emission tomography and temporal changes in morphology by intravascular ultrasound in cardiac transplant recipients. *J Heart Lung Transplantation* 1999;18:211-219 996.83, V42.1 AUC indication(s) 15

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with suspected or known coronary disease being evaluated for cardiovascular risk prior to non-cardiac surgery, who meet the recommendations for PET set forth in the clinical guidelines of the ASNC and the ACC. Patient undergoing interme-diate risk noncardiac or vascular surgery, who is unable to exercise	V72.80–72.84	AUC indication(s) 43 and 47

Diagnostic literature supporting cardiac PET study

[1] ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging— executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). http://www.ncbi.nlm.nih.gov/ pubmed/14522503

[2] Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology. *J Am Coll Cardiol.* 2003 Oct 1;42(7):1318-33

[3] Beanlands R, Dick A, Chow B, et al. CCS; CAR; CANM; CNCS; and Can SCMR Position

[4] Statement on Advanced Noninvasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease. *Can J Cardiol.* 2007 Feb;23(2):107-19

[5] Cerqueira MD, Allman KC, Ficaro EP, et al. ASNC Information Statement— Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiology* 2010;17:709-18

[6] ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol.* 2009 Nov 2;54:13-118

Patients at intermediate or high risk of CAD with syncope to determine the presence and functional severity of potential coronary disease	780.2	AUC indication(s) 21

Diagnostic literature supporting cardiac PET study

[1] Hendel RC, Berman DS, MD, Di Carli MF, et al. ACCF/ ASNC/ACR/AHA/ASE/ SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging. *J. Am. Coll. Cardiol.* 2009;53;2201-2229

[2] Hendel RC, Abbott BG, Bateman TM, Blankstein R, Calnon DA, et al. ASNC Information Statement. The role of radionuclide myocardial perfusion imaging for asymptomatic individuals. *J Nucl Cardiol* 2011;18(1):3-15

Patients presenting to the emergency department with acute chest pain, to evaluate the possibility of an acute coronary syndrome	413.9, 786.50–786.59, 786.05–786.09	AUC indication(s) 6, 7, 8, and 9

Diagnostic literature supporting cardiac PET study

[1] Di Carli, MF, Dorbala, S, Meserve, J, El Fakhri, G, Sitek, A, & Moore, SC. Clinical Myocardial Perfusion PET/CT. J Nucl Med. 2007;48(5):783-793 413.9, 786.50–786.59, 786.05–786.09 AUC indication(s) 6, 7, 8, and 9 Use of Cardiac PET in Women at intermediate or high risk for CAD

Use of Cardiac PET in Women at intermediate or high risk for CAD	413.9, 414.8–414.9, 786.05–786.09, 786.50–786.59	AUC indication(s) 3, 4, and 5

Diagnostic literature supporting cardiac PET study

[1] Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. http://www.ncbi.nlm.nih. gov/pubmed/16464714[Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, Hertenstein GK, Moutray KL, Reid K, Cullom SJ. *J Nucl Cardiol.* 2006 Jan-Feb;13(1):24-33

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
To assess flow quantification and flow reserve in patients with known or suspected CAD		AUC does not address this, but it is supported by ASNC guidelines. PET Myocardial Perfusion and Glucose Metabolism Imaging

Diagnostic literature supporting cardiac PET study

[1] Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med.* 1994 Jun 23;330(25):1782-8

[2] Beanlands R, Muzik O, Melon P, Sutor R, Sawada S, Muller D, Bondie D, Hutchins GD, Schwaiger M. Noninvasive quantification of regional myocardial flow reserve in stenosed and angiographically normal vessels of patients with coronary atherosclerosis. *J Am Coll Cardiol* 1995;26(6):1465-1475

[3] Muzik O, Duvernoy C, Beanlands RSB, Sawada S, Dayanikli F, Wolfe ER, Schwaiger M. Assessment of the diagnostic performance of quantitative flow measurements in normals and patents with angiographically documented CAD using [N- 13] ammonia and PET. *J Am Coll Cardio*l 1998;31:534-40

[4] Parkash R, de Kemp RA, Ruddy TD, Kitsikis A, Hart R, Beauschene L, Williams K, Davies RA, Labinaz M, Beanlands RSB. Potential utility of perfusion quantification using rubidium-82 PET in patients with three-vessel coronary artery disease measured using rubidium-82 PET. *J Nucl Cardiol* 2004; 11(4):440-449

[5] Anagnostopoulos C, Almonacid A, El Fakhri G, Curillova Z, Sitek A, Roughton M, Dorbala S, Popma JJ, Di Carli MF. Quantitative relationship between coronary vasodilator reserve assessed by ^{82}Rb PET imaging and coronary artery stenosis severity. *Eur J Nucl Med Mol Imaging*. 2008 Sep;35(9):1593- 601

[6] Hajjiri MM, Leavitt MB, Zheng H, Spooner AE, Fischman AJ, Gewirtz H. Comparison of positron emission tomography measurement of adenosine-stimulated absolute myocardial blood flow versus relative myocardial tracer content for physiological assessment of coronary artery stenosis severity and location. *JACC Cardiovasc Imaging.* 2009 Jun;2(6):751-8

Value of PET in nondiagnostic SPECT MPI		AUC does not address this, but it is supported by ASNC Guidelines PET myocardial perfusion and glucose metabolism imaging

Diagnostic literature supporting cardiac PET study

[1] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029- 1039

[2] Bateman, T. M., Heller, G. V., McGhie, A. I., Friedman, J. D., Case, J. A., Bryngelson, J. R., et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc-99m sestamibi SPECT. *Journal of Nuclear Cardiology.* 2006;13(1):24-33

Value of PET imaging to determine multivessel disease		AUC does not address this, but it is supported by ASNC Guidelines PET myocardial perfusion and glucose metabolism imaging

Diagnostic literature supporting cardiac PET study

[1] Demer LL, Gould KL, Goldstein R, et al. Assessment of coronary artery disease severity by positron emission tomography: comparison with quantitative angiography in 193 patients. *Circulation* 1989;79:825- 835

[2] Dorbala S, Hachamovitch R, Curillova Z. Incremental prognostic value of gated rubidium-82 positron emission tomography over clinical variables and rest left ventricular ejection fraction. *J Am Coll Cardiol Img* 2009;2:846-854

[3] Sampson Uk, Dorbala S, Kwong R, Di Carli M. Diagnostic Accuracy of Rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. *J Am Coll Cardiol* 2007;49:1052-1058

[4] Bateman TM, Heller GV, McGhie AI et al. Diagnostic accuracy of rest/stress ECGgated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc99m sestamibi SPECT. *J Nucl Cardiol* 2006;13:24- 33

[5] Parkash r, De Kemp RA, Ruddy TD, Beanlands RSB et al. Potential Utility of rubidium-82 PET quantification in patients with three-vessel coronary disease. *J Nucl Cardiol* 2004;11: 440-449

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
PET imaging in obese patients		AUC does not address this, but it is supported by ASNC Guidelines PET myocardial perfusion and glucose metabolism imaging

Diagnostic literature supporting cardiac PET study

[1] Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc- 99m sestamibi SPECT. http://www.ncbi.nlm.nih.gov/ pubmed/16464714[Bateman TM, Heller GV,McGhie AI,FriedmanJD, Case JA,BryngelsonJR,HertensteinGK, Moutray KL,ReidK,Cullom SJ. *J Nucl Cardiol.* 2006 Jan Feb;13(1):24-33

[2] ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). http://www.ncbi.nlm.nih.gov/pubmed/14522503[Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology. *J Am Coll Cardiol.* 2003 Oct 1;42(7):1318-33

[3] CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease—executive summary. http://www.ncbi.nlm.nih.gov/pubmed/17311116 [Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M, Leong-Poi H, Miller RM, Nichol G, Freeman M, Bogaty P, Honos G, Hudon G, Wisenberg G, Van Berkom J, Williams K, Yoshinaga K, Graham J; Canadian Cardiovascular Society; Canadian Association of Radiologists; Canadian Association of Nuclear Medicine; Canadian Nuclear Cardiology Society; Canadian Society of Cardiac Magnetic Resonance. *Can J Cardiol.* 2007 Feb;23(2):107-19

[4] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039

Indications for PET for prognostic purposes[1]

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with high probability of CHD based on clinical findings and risk factors who are having PET to define the extent and severity of CAD for prognostic purposes	414.01	AUC indication(s) 15

Diagnostic literature supporting cardiac PET study

[1] Dorbala S, Hachamovitch R, Curillova Z, Thomas D, Vangala D, Kwong RY, Di Carli MF. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *J Am Coll Cardiol Img* 2009;2:846-854

[2] Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, Burkhard N, Wyss CA, Kaufmann PA. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography: added value of coronary flow reserve. *J Am Coll Cardiol* 2009;54:150-156

[3] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753

[4] Cecchi, F., Olivotto, I., Gistri, R., Lorenzoni, R., Chiriatti, G., & Camici, P. G. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *New England Journal of Medicine.* 2003;349(11):1027-1035

[5] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok- Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039

Selected asymptomatic high risk subgroups may also be candidates for PET; these include, but are not limited to, high risk diabetics, patients with chronic kidney disease, and patients with strong family history of CAD	414.01	AUC indication(s) 15

Diagnostic literature supporting cardiac PET study

Studies using cardiac PET to follow improvement of disease in high risk patients:

[1] Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of testing in coronary endothelium. *Circulation* 1994;89:1530-8

[2] Coronary microvascular function in early chronic kidney disease. Chorytan DM, DiCarli MF. Circulation Cardiovascular Imaging 2010;3:66307

[3] Diyridamole cold pressor test and demonstration of endovascular dysfunction: a PET study of myocardial perfusion in diabetes. Kjoer A, Meyer C, Nielsen F, et al. *J Nucl Med* 2003;44:19-23

[4] Reduced myocardial flow reserve in non-insulin dependent diabetes mellitus. Yokoyama F, Momomwia S, Ohtake T. et al. *J Am Coll Cardiol* 1997;30:1472-1477

[5] Hendel RC, Abbott BG, Bateman TM, Blankstein R, Calnon DA, et al. ASNC Information Statement. The role of radionuclide myocardial perfusion imaging for asymptomatic individuals. *J Nucl Cardiol* 2011;18(1):3-15

Patients with an abnormal imaging stress test with new/worsening symptoms or with prior equivocal results who are having PET to determine the extent of ischemia to guide future therapy	414.0, 413.9, 414.8, 786.09, 786.50	AUC indication(s) 29 and 30

Diagnostic literature supporting cardiac PET study

[1] What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? http://www.ncbi. nlm.nih.gov/pubmed/16949498[Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin Szeto A, Aung M, Davies RA, Ruddy TD, Beanlands RS. *J Am Coll Cardiol.* 2006 Sep 5;48(5):1029-39. Epub 2006 Aug 17

[2] Chow B, Al-Shammeri OM, Beanlands R, Chen L, deKemp RA, DaSilva J, Ruddy T. Prognostic Value of Treadmill Exercise and Dobutamine Stress Positron Emission Tomography. *Can J Cardiol.* 2009 Jul;25(7):e220-4

[3] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039

[4] Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, Bengel FM. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical ^{82}Rb PET perfusion imaging. *J Nucl Med.* 2011 May;52(5):726-32

[5] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with known CAD who have new onset of angina, angina equivalents, or significant change in symptoms	411.0, 412, 413.9, 786.50, 786.51, 786.59, 786.05	AUC indication(s) 4, 5, 30, and 31

Diagnostic literature supporting cardiac PET study

[1] What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? http://www.ncbi.nlm.nih.gov/pubmed/16949498[Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin Szeto A, Aung M, Davies RA, Ruddy TD, Beanlands RS. *J Am Coll Cardiol.* 2006 Sep 5;48(5):1029-39. Epub 2006 Aug 17

[2] Chow B, Al-Shammeri OM, Beanlands R, Chen L, deKemp RA, DaSilva J, Ruddy T. Prognostic Value of Treadmill Exercise and Dobutamine Stress Positron Emission Tomography. *Can J Cardiol.* 2009 Jul;25(7):e220-4

[3] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039

[4] Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, Bengel FM. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical ^{82}Rb PET perfusion imaging. *J Nucl Med.* 2011 May;52(5):726-32

[5] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753

Patients with a history of CAD and recent myocardial infarction in whom PET is performed to define the presence of post-MI ischemia, myocardium at risk, assess myocardial viability, and assess LV function (using gated PET techniques)	414.0–414.07, 411, 410–410.92, 428.00–428.90	AUC indication(s) 50, 52, and 62

Diagnostic literature supporting cardiac PET study

[1] D'EgidioG, Nichol G, Williams KA,Guo A, Garrard L, deKemp R, Ruddy TD, DaSilva J, HumenD,GulenchynKY, FreemanM,Racine N,BenardF,Hendry P,BeanlandsRS; PARR-2 Investigators. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *JACC Cardiovasc Imaging.* 2009 Sep;2(9):1060-8. PubMed PMID: 19761983

[2] Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, Gulenchyn KY, Garrard L, deKemp R, Guo A, Ruddy TD, Benard F, Lamy A, Iwanochko RM; PARR-2 Investigators. F-18-fluorodeoxyglucose positron emission tomography imagingassisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol.* 2007 Nov 13;50(20):2002-12. Epub 2007 Oct 10. PubMed PMID: 17996568

[3] Gould KL, Yoshida K, Hess MJ, Haynie M, Mullani N, Smalling RW. Myocardial metabolism of fluorodeoxyglucose compared to cell membrane integrity for the potassium analogue rubidium-82 for assessing infarct size in man by PET. *J Nucl Med.* 1991 Jan;32(1):1-9. PMID: 1988610

[4] Yoshida K, Gould KL. Quantitative relation of myocardial infarct size and myocardial viability by positron emission tomography to left ventricular ejection fraction and 3-year mortality with and without revascularization. *J Am Coll Cardiol.* 1993 Oct;22(4):984-97. PMID: 8409073

[5] Maes A, Van de Werf F, Nuyts J, Bormans G, Desmet W, Mortelmans L. Impaired myocardial tissue perfusion early after successful thrombolysis. Impact on myocardial flow, metabolism, and function at late follow-up. *Circulation.* 1995 Oct 15;92(8):2072-8. PubMed PMID: 7554184

Patients with acute Coronary syndromes who have become stable on medical therapy and are undergoing PET to assess ischemic burden on medical therapy, and whether or not angiography and revascularization are indicated	786.50–786.59, 414.0–414.07, 411	AUC indication(s) 50 and 52

Diagnostic literature supporting cardiac PET study

[1] Chow B, Al-Shammeri OM, Beanlands R, Chen L, deKemp RA, DaSilva J, Ruddy T. Prognostic Value of Treadmill Exercise and Dobutamine Stress Positron Emission Tomography. *Can J Cardiol.* 2009 Jul;25(7):e220-4

[2] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039

[3] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with poor functional capacity which is felt to be an independent marker of coronary risk to assess for presence of significant CAD	786.05–786.09	AUC criterion(s) 15
Diagnostic literature supporting cardiac PET study [1] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753		
Risk assessment of patients with test results and/or known chronic stable CAD	410–410.92, 411, 412, 413.9, 414.0–414.07, 414.8–414.90, 429.10, 786.05–786.09, 786.50–786.59, 794.30	AUC does not address this, but it is supported by ASNC guidelines PET myocardial perfusion and glucose metabolism imaging standardized reporting of radionuclide myocardial perfusion and function
Diagnostic literature supporting cardiac PET study [1] Chow B, Al-Shammeri OM, Beanlands R, Chen L, deKemp RA, DaSilva J, Ruddy T. Prognostic Value of Treadmill Exercise and Dobutamine Stress Positron Emission Tomography. *Can J Cardiol.* 2009 Jul;25(7):e220-4 [2] Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin SA, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006 September 5;48(5):1029-1039 [3] Kirkeith Lertsburapa, Alan W. Ahlberg, Timothy M. Bateman, Deborah Katten and Lyndy Volker, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *Circulation* 2008;15;745-753		
Subgroup 2: asymptomatic patients at least 2 years post-PCI	410–410.92, 411, 412, 413.9, 414.0–414.07, 414.8–414.90, 429.10, 786.05–786.09, 486.50–786.59, 794.30	AUC indication(s) 60
Diagnostic literature supporting cardiac PET study [1] Van Tosh A, Garza D, Roberti R, Sherman W, Pompliano J, Ventura B, Horowitz SF. Serial myocardial perfusion imaging with dipyridamole and rubidium-82 to assess restenosis after angioplasty. *J Nucl Med.* 1995 Sep;36(9):1553-60. PMID: 7658209 [2] Rimoldi O, Burns SM, Rosen SD, Wistow TE, Schofield PM, Taylor G, Camici PG. Measurement of myocardial blood flow with positron emission tomography before and after transmyocardial laser revascularization. *Circulation.*1999 Nov 9;100(19 Suppl):II134-8. PubMed PMID: 10567292 [3] Neumann FJ, Kósa I, Dickfeld T, Blasini R, Gawaz M, Hausleiter J, Schwaiger M, Schömig A. Recovery of myocardial perfusion in acute myocardial infarction after successful balloon angioplasty and stent placement in the infarct-related coronary artery. *J Am Coll Cardiol.* 1997 Nov 1;30(5):1270-6. PMID: 9350926		
Subgroup 3: asymptomatic patients at least 5 years post-coronary bypass surgery	410–410.92, 411, 412, 413.9, 414.0–414.07, 414.8–414.90, 429.10, 786.05–786.09, 486.50–786.59, 794.30	AUC indication(s) 58
Diagnostic literature supporting cardiac PET study [1] Marwick TH, Lafont A, Go RT, Underwood DA, Saha GB, MacIntyre WJ. Identification of recurrent ischemia after coronary artery bypass surgery: a comparison of positron emission tomography and single photon emission computed tomography. *International Journal of Cardiology* 1992;35:33-41		

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
Patients with known coronary disease and left ventricular dysfunction who are having PET to identify the presence of myocardial viability and determine suitability for revascularization procedures	410–410.92, 410.0–.410.9, 412.	AUC indication(s) 62

Diagnostic literature supporting cardiac PET study

[1] Beanlands R, Dick A, Chow B, et al. CCS; CAR; CANM; CNCS; and CanSCMR Position Statement on Advanced Noninvasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease. *Can J Cardiol.* 2007 Feb;23(2):107-19

[2] Schinkel, A. F., Poldermans, D., Elhendy, A., & Bax, J. J. (2007). Assessment of myocardial viability in patients with heart failure. *Journal of Nuclear Medicine*, 48(7), 1135-1146

[3] Eitzman, D., al-Aouar, Z., Kanter, H. L., vom Dahl, J., Kirsh, M., Deeb, G. M., et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. *Journal of the American College of Cardiology.* 1992;20(3):559-565

[4] Abraham A, Nichol G, Williams KA, Guo A, deKemp RA, Garrard L, Davies RA, Duchesne L, Haddad H, Chow B, DaSilva J, Beanlands RS; PARR 2 Investigators. ^{18}F-FDG PET imaging of myocardial viability in an experienced center with access to ^{18}F-FDG and integration with clinical management teams: the Ottawa-FIVE substudy of the PARR 2 trial. *J Nucl Med.* 2010 Apr;51(4):567-74

[5] D'Egidio G, Nichol G, Williams KA, Guo A, Garrard L, deKemp R, Ruddy TD, DaSilva J, Humen D, Gulenchyn KY, Freeman M, Racine N, Benard F, Hendry P, Beanlands RS; PARR-2 Investigators. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *JACC Cardiovasc Imaging.* 2009 Sep;2(9):1060-8

To define functional severity of known CAD by prior testing such as coronary angiography or coronary CTA	746.8–746.89, 429.2, 414.8–414.90, 414.0–414.07	AUC indication(s) 32

Diagnostic literature supporting cardiac PET study

[1] Kirkeeide R, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial imaging during coronary vasodilation. VII. Validation of coronary flow reserve as a single integrated measure of stenosis severity accounting for all its geometric dimensions. *J Am Coll Cardiol* 1986;7:103-13

[2] Gould KL, Goldstein RA, Mullani N, et al. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. VIII. Feasibility of 3D cardiac positron imaging without a cyclotron using generator produced Rb-82. *J Am Coll Cardiol* 1986;7;775-92

[3] Kajander S, Joutsiniemi E, Saraste M, Pietila M, Ukkonen H, Saraste A, Sipila HT, Teras M, Maki M, Airaksinen J, Hartiala J, Knuuti J. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation* 2010;122:603-613

Patients who have coronary calcification on CT scan which is quantified by an Agatston score greater than, or equal to, 100	414.01	AUC scores of 34, 35, and 36

Diagnostic literature supporting cardiac PET study

[1] Bybee KA, Lee J, Markiewicz R, Bateman TM. Diagnostic and Clinical Benefit of combined coronary calcium assessment and perfusion assessment in patients undergoing PET/CT myocardial perfusion stress imaging. *J Nucl Cardiol* 2010;17:188-196

[2] Schenker mP, Dorbala S, Hong ECT, Hachamovitch R, Di Carli M. Interrelation of Coronary calcification, myocardial ischemia and outcomes in patients with intermediate likelihood of coronary artery disease. *Circulation* 2008;117:1696-1700

[3] Fathala A, Alliefri A, Abouzied M. Coronary artery calcification by PET/CT as a marker of myocardial ischemia/coronary artery disease. *Nuclear Medicine Communications* 2011;32:273-278

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
To assess flow quantification and flow reserve in patients with known or suspected CAD		AUC does not address this, but it is supported by ASNC guidelines PET myocardial perfusion and glucose metabolism imaging Standardized reporting of radionuclide myocardial perfusion and function

Diagnostic literature supporting cardiac PET study

[1] Tio RA, Dabeshlim A, Siebelink HM, de Sutter J, Hillege HL, Zeebregts CJ, Dierckx RA, van Veldhuisen DJ, Zijlstra F, Slart RH. Comparison between the prognostic value of left ventricular function and myocardial perfusion reserve in patients with ischemic heart disease. *J Nucl Med.* 2009 Feb;50(2):214-9

[2] Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, Burkhard N, Wyss CA, Kaufmann PA. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol.* 2009 Jul 7;54(2):150-6

[3] Ziadi MC, deKemp RA, Williams KA, Guo A, Chow BJW, Renaud JM, Ruddy TD, Sarveswaran N, Tee RE, Beanlands RS. Impaired Myocardial Flow Reserve on Rubidium-82 Positron Emission Tomography Imaging Predicts Adverse Outcomes In Patients Assessed for Myocardial Ischemia. *J Am Coll Cardiol.* 2011 (in press)

[4] Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, Bengel FM. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical ^{82}Rb PET perfusion imaging. *J Nucl Med.* 2011 May;52(5):726-32

[5] Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011 Nov 15;124(20):2215-24

PET to assess the efficacy of medical therapy for reduction of inducible myocardial ischemia	414.0–414.07, 414.8–414.90	AUC does not address this, but it is supported by ASNC guidelines PET myocardial perfusion and glucose metabolism imaging

Diagnostic literature supporting cardiac PET study

[1] Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Shortterm cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of healing coronary endothelium. *Circulation.* 1994 Apr;89(4):1530-8. PMID: 8149518

[2] Sdringola S, Nakagawa K, Nakagawa Y, Yusuf SW, Boccalandro F, Mullani N, Haynie M, Hess MJ, Gould KL. Combined intense lifestyle and pharmacologic lipid treatment further reduce coronary events and myocardial perfusion abnormalities compared with usual-care cholesterol-lowering drugs in coronary artery disease. *J Am Coll Cardiol.* 2003 Jan 15;41(2):263-72. PMID: 12535820

[3] Gould KL, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, Mullani N, Bolomey L, Dobbs F, Armstrong WT, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA.* 1995 Sep 20;274(11):894-901. PMID: 7674504

[4] Huggins GS, Pasternak RC, Alpert NM, Fischman AJ, Gewirtz H. Effects of shortterm treatment of hyperlipidemia on coronary vasodilator function and myocardial perfusion in regions having substantial impairment of baseline dilator reverse. *Circulation.* 1998 Sep 29;98(13):1291-6. PMID: 9751677

[5] Yoshinaga K, Beanlands RS, deKemp RA, Lortie M, Morin J, Aung M, McKelvie R, Davies RF. Effect of exercise training on myocardial blood flow in patients with stable coronary artery disease. *Am Heart J* 2006 June;151(6):1324-1328

PET following coronary revascularization in patients with recurrent anginalike symptoms	413.9, 786.5, 411, 786.05–786.09, 780.02, 414.0–414.07, 414.8–414.90, V45.81, V45.82	AUC indication(s) 55

Diagnostic literature supporting cardiac PET study

[1] Van Tosh A, Garza D, Roberti R, Sherman W, Pompliano J, Ventura B, Horowitz SF. Serial myocardial perfusion imaging with dipyridamole and rubidium-82 to assess restenosis after angioplasty. *J Nucl Med.* 1995 Sep;36(9):1553-60. PMID:7658209

[2] Rimoldi O, Burns SM, Rosen SD, Wistow TE, Schofield PM, Taylor G, Camici PG. Measurement of myocardial blood flow with positron emission tomography before and after transmyocardial laser revascularization. *Circulation.* 1999 Nov 9;100(19 Suppl):II134-8. PubMed PMID: 10567292

[3] Neumann FJ, Kósal, Dickfeld T, Blasini R, Gawaz M, Hausleiter J, Schwaiger M, Schömig A. Recovery of myocardial perfusion in acute myocardial infarction after successful balloon angioplasty and stent placement in the infarct-related coronary artery. *J Am Coll Cardiol.* 1997 Nov 1;30(5):1270-6. PMID: 9350926

Appropriate Clinical indications for conducting a cardiac PET study	ICD-9 code	AUC which supports conducting a cardiac PET study
PET following coronary revascularization in patients with recurrent angina like symptoms	413.9, 786.5, 411, 786.05–786.09, 780.02, 414.0–414.07, 414.8–414.90, V45.81, V45.82.	AUC indication(s) 56

Diagnostic literature supporting cardiac PET study

[1] Goldstein RA, Kirkeeide RL, Smalling RW, Nishikawa A, Merhige ME, Demer LL, Mullani NA, Gould KL. Changes in myocardial perfusion reserve after PTCA: noninvasive assessment with positron tomography. *J Nucl Med.* 1987 Aug;28(8):1262-7. PMID: 2956379

Reference

1 Heller, GV, Beanlands R, Merlino DA, Travin MI, Calnon DA, Dorbala S, Hendel RC, Mann A, Bateman TM, Van Tosh A., ASNC model coverage policy: Cardiac postiron emission tomographic imaging. *J Nucl Cardiol.* 2013 Oct;20(5):916-47. doi: 10.1007/s12350-013-9754-7.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection.

Fludeoxyglucose F 18 Injection, USP
For intravenous use
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.2)	7/2010
Adverse Reactions (6)	7/2010

INDICATIONS AND USAGE

Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).

The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi in the neurology setting (2.2).

Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

DOSAGE FORMS AND STRENGTHS

Multi-dose 30mL and 50mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose
F 18 Injection and 4.5mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration (3).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose adnormalities: may cause suboptimal imaging (5.2).

ADVERSE REACTIONS

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).

- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

1.1 Oncology

For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

1.2 Cardiology

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

1.3 Neurology

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

2.1 Recommended Dose for Adults

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

2.2 Recommended Dose for Pediatric Patients

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [see Use in Special Populations (8.4)].

2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F18 Injection facilitates localization of cardiac ischemia

2.4 Radiation Dosimetry

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human[2] data and using the data published by the International Commission on Radiological Protection[4] for Fludeoxyglucose ^{18}F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

Table 1. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F-18 Injection[a]

Organ	Newborn (3.4 kg)	1-year old (9.8 kg)	5-year old (19 kg)	10-year old (32 kg)	15-year old (57 kg)	Adult (70 kg)
Bladder wall[b]	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.8	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall *	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Small intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall **	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone surface	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.09	0.078	0.072	0.070
Other tissues	0.59	0.25	0.13	0.083	0.052	0.042

[a] MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallagher et al.1 and Jones et al.2

[b] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used. *LLI = lower large intestine; **ULI = upper large intestine

2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection 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.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

2.6 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

2.7 Imaging Guidelines

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. 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)].

5.2 Blood Glucose Abnormalities

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

6 ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

7 DRUG INTERACTIONS

The possibility of interactions of Fludeoxyglucose F 18 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 Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

8.3 Nursing Mothers

It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in women who are breast-feeding. Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding.

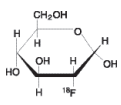
8.4 Pediatric Use

The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. In the oncology or cardiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

11 DESCRIPTION

11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[^{18}F]fluoro-D-glucose has the molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.26, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40GBq (20.0 to 200 mCi) of 2-deoxy-2-[^{18}F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics

Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 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. Pricipal Radiation Emission Data for Fluorine F18

Radiation/Emission	% Per Disintegration	Mean Energy
Positron (b+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35 x 10-6 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

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

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

Table 4. Physical Decay Chart for Fluorine F18

Minutes	Fraction Remaining
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [^{18}F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the ‚lumped constant" ratio), Fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

12.2 Pharmacodynamics

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial sub strate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these condi-

tions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

12.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min.

Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to [^{18}F]-FDG-6- phosphate at a rate proportional to the rate of glucose utilization within that tissue. [F18]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F18]fluoro-6-phospho-D-mannose([F 18]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (ClDG)). Biodistribution and metabolism of ClDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

Elimination: Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. Within 33 minutes, a mean of 3.9% of the administrated radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations:

The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [see Warnings and Precautions (5.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known.

Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES

1. Gallagher B.M., Ansari A., Atkins H., Casella V., Christman D.R., Fowler J.S., Ido T., MacGregor R.R., Som P., Wan C.N., Wolf A.P., Kuhl D.E., and Reivich M. "Radiopharmaceuticals XXVII. 18F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals," J Nucl Med, 1977; 18, 990-6.
2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," J Nucl Med, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-I 1026, 89.
4. ICRP Publication 53, Volume 18, No. l-4,1987, pages 75-76.

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[F 18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:

- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

Manufactured by: PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

Distributed by: PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

PETNET Solutions

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March 1, 2011

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 (The total volume in the vial will vary) (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 PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at 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: 11/2011

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DRUG PRODUCT LABEL

*** 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	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	00013	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 (30 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 (the total volume in the vial will vary) 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.

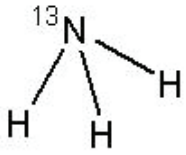
8.4 Pediatric Use

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

- Annals of the ICRP. Publication 53. Radiation dose to patients from radiopharmaceuticals. New York: Pergamon Press, 1988.
- 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 30 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. The total volume in the vial will vary. 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.

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