Doc. 1

Van: meldpunt@igz.nl
Aan: meldpunt@igz.nl
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^{13}N-ammonia and $H_2{}^{15}O$ PET/CT of Myocardial Perfusion

P. Raijmakers, VUmc Amsterdam

1. Introduction

Coronary artery disease (CAD) is a major cause of death in the modern world. The diagnosis of CAD is mainly focused on the detection of obstructive epicardial coronary stenosis. Positron emission tomography (PET) is widely accepted as a diagnostic technique which can be used to assess myocardial perfusion. Three PET tracers have been validated (Table 1) for assessing myocardial perfusion. $H_2{}^{15}O$ is characterized by different kinetic properties as compared with $^{13}NH_3$, and ^{82}Rb. The latter tracers become metabolically trapped while cleared from the intravascular compartment, yielding excellent qualitatively gradable imaging due to high tissue-to-background ratios. In contrast, $H_2{}^{15}O$ is a freely diffusible, metabolically inert tracer that promptly reaches equilibrium between blood and tissue, thus is not accumulated in the myocardium. As a consequence, direct radiotracer distribution images of $H_2{}^{15}O$ are of little diagnostic value. In recent years, however, improved techniques and parametric imaging by automated software packages, have generated qualitatively gradable $H_2{}^{15}O$ perfusion images comparable to $^{13}NH_3$, and ^{82}Rb. Meta-analyses comparing myocardial PET to SPECT and cardiovascular magnetic resonance imaging (CMR),demonstrate that MPI with PET yields the highest diagnostic accuracy. The majority of clinical studies on the diagnostic accuracy of detection of obstructive CAD have been conducted with static uptake images of ^{82}Rb and $^{13}NH_3$. Weighted sensitivity, specificity, NPV, and PPV were 91, 86, 81, and 93%, respectively. Furthermore, cardiac PET imaging can potentially be used to study subendocardial perfusion. Myocardial ischaemia occurs principally in the subendocardial layer, whereas conventional myocardial perfusion imaging provides no information on the transmural myocardial blood flow (MBF). In a recent $H_2{}^{15}O$ PET study a significantly decreased subendocardial MBF was found in ischaemic myocardium.

Table 1. Characteristics of $H_2{}^{15}O$, $^{13}NH_3$, and ^{82}Rb for PET myocardial perfusion imaging.

	$H_2{}^{15}O$	$^{13}NH_3$	^{82}Rb	Comment
Half-life	123 sec	9,97 min	76 sec	Mandatory on-site production of the tracers given their short physical half-life

Production	Cyclotron	Cyclotron	Generator	Generator equipment have lower installation and maintenance costs
Kinetics	Freely diffusible, metabolically inert	Metabolically trapped in myocardium	Metabolically trapped in myocardium	Complete extraction from bloodpool into myocardial tissue renders $H_2{}^{15}O$ an ideal perfusion tracer
Mean positron range in tissue	1,1 mm	0,4 mm	2,8 mm	^{82}Rb 's higher tissue penetration depth limits the spatial resolution of the perfusion imaging
Dose	0,00093 mSv/ MBQ	0,002 mSv/ MBq	0,0034 mSv/ MBq	

Quantification of myocardial perfusion with PET

Dynamic PET acquisition protocols allows quantification of stress and rest myocardial blood flow (MBF in units of $mL \cdot min^{-1} \cdot g^{-1}$ and calculation of coronary flow reserve (CFR). Literature suggests that quantitative analysis is superior to static uptake image evaluation. Furthermore, hyperaemic MBF assessment seems to outperform CFR for the diagnosis of obstructive CAD, which may result in stress only protocols. Thresholds for what should be considered pathological hyperaemic MBF or CFR are unfortunately not uniform. MBF is related to age, sex, and cardiovascular risk profile. Perfusion thresholds will be tracer specific and may require correction for individual patient characteristics. Ongoing studies are targeted to addressing these issues. Use of a single cut-off may be a simplification of the underlying pathophysiology, as MBF is determined by the combination of epicardial coronary flow and microvascular vasomotor function. In terms of prognosis, the quantitative nature of PET has shown incremental value. The extent and severity of (reversible) perfusion defects diagnosed with PET holds strong prognostic information beyond traditional cardiovascular risk factors. Of particular interest is the fact that apparently normal perfusion images with a homogenous tracer distribution can be reclassified based on diffusely abnormal hyperaemic MBF or CFR. Several studies have revealed that this subset of patients is at increased risk for future cardiac events.

Coronary computed tomography angiography (CCTA)

CCTA is a promising tool for non-invasive evaluation of coronary anatomy. Pooled analysis of the currently available literature demonstrates a high sensitivity (96%) and negative predictive value (NPV, 94%), rendering it a clinically useful tool to rule out obstructive coronary stenosis. However, despite its non-invasive nature and high sensitivity, CCTA is not able to determine the haemodynamic relevance for a given epicardial coronary stenosis. Indeed, several studies have clearly demonstrated the disconcordancy between the anatomical and functional aspects of coronary atherosclerosis, emphasizing the role of myocardial perfusion imaging (MPI) in the non-invasive evaluation of CAD. In recent years there has been a fast evolution of the hybrid imaging technique, incorporating multidectector-row CT with PET detector techniques.

Hybrid Cardiac PET/CT

Hybrid cardiac PET/CT imaging enables the near simultaneous evaluation of coronary anatomy and (quantitative) myocardial perfusion in a single scanning session, which can be performed within 30-60 min. Although the number of diagnostic studies on the accuracy of hybrid cardiac PET/CCTA is small, they demonstrate an improved diagnostic performance as compared with either imaging modality alone. Three studies have evaluated the diagnostic value of hybrid PET/CCTA over stand-alone CCTA and PET MPI. Hybrid imaging is shown to be particularly useful for enhancing specificity and PPV of CCTA, although significant rises in these parameters can also be observed when compared to PET alone.

The hybrid cardiac PET/CT imaging results, generally categorize patients into one of four groups. The first category represents patients with a normal CCTA and a normal MBF/CFR, confirming a normal coronary circulation. Secondly, a normal CCTA combined with a decreased MBF and/or CRF represents coronary microvascular dysfunction. Hence, a completely normal CCTA can rule out epicardial atherosclerotic disease, but may need conformation of normal hyperaemic MBF and CFR to rule out coronary microvascular dysfunction.

An abnormal CCTA, compatible with obstructive CAD, warrants confirmation with perfusion imaging to determine its actual haemodynamic relevance and MPI should act as a gatekeeper for further invasive testing. A third group, representing patients with an abnormal CCTA and a decreased MBF, may benefit from revascularization. Not only the presence of ischaemia, but also the extent of the jeopardized area is important. Revascularization in patients with mild to moderate ischaemic burden (i.e. <10% of the myocardium) does not alter outcome, yet alleviate symptoms. Satisfactorily medically controlled anginal symptoms therefore justify a conservative approach and a potentially hazardous invasive procedure should be deferred. Drug refractory angina and / or large ischaemic burden, seems to warrant revascularisation. This topic is, however, still a matter of debate and further studies are needed. Lastly, patients with an abnormal CCTA and a normal MBF may benefit from optimal medical treatment. With the implementation of cardiac hybrid PET/CT protocols, a more pragmatic referral of patients to the catheterisation laboratory may be achieved, thus minimising the need for invasive diagnostic procedures.

2. Methodology

This review is based on available scientific literature on the subject.

3. Indications

Hybrid PET/CT:

Evaluation of patients with an intermediate likelihood of CAD, for diagnosis of CAD, including location and severity of CAD and extent of ischaemic area.

Additional indications

Myocardial Perfusion PET:

- Assessment of regional perfusion in the presence of obstructive coronary artery disease

Absolute contraindications for adenosine stress myocardial perfusion imaging with PET:

- Unstable angina/acute coronary syndrome,
- Severe bronchospasms
- Second or third-degree heart block or sick sinus syndrome, without a pacemaker
- Symptomatic aortic stenosis and hypertrophic obstructive cardiomyopathy
- Systolic blood pressure <90 mmHg
- Cerebral ischaemia
- Persantin/dipyridamol use in the 24 h before adenosine stress test

Relative contraindications to vasodilator stress tests are:

- Severe sinus bradycardia (heart rate <40/min)
- Severe atherosclerotic laesions of extracranial artery

4. Relation to other diagnostic procedures/therapies

Several techniques can be used to evaluate CAD, including CCTA, cardiac MRI, myocardial SPECT and stress echocardiography. Owing to the quantitative nature, routine use of attenuation correction, higher spatial resolution, shorter study protocols, and lower radiation exposure, cardiac PET surpasses SPECT MPI both in terms of diagnostic accuracy and patient convenience. However, comprehensive 'head to head' studies comparing diagnostic accuracy of imaging techniques regarding the detection of CAD and abnormal MBF are scarce. More clinical research is needed regarding efficient diagnostic strategies for detection of obstructive CAD. Furthermore, there are three PET perfusion tracers available for myocardial perfusion imaging: $^{13}NH_3$, $H_2{}^{15}O$ and ^{82}Rb. These are all short-lived tracers that require on-site production. ^{82}Rb has the advantage of being generator produced, avoiding the need for an on-site cyclotron. However, ^{82}Rb's longer positron range and lower count statistics due to the ultra-short half-life (76 sec) compromise image resolution (see also table 1 for comparison of the PET tracers).

5. Medical information necessary for planning

- Information which should be available prior to planning of the procedure:
- Indication for diagnostic cardiac PET and/or CT
- body mass
- ability to lie still for approximately 45 min (in case of $H_2{}^{15}O$ PET/CT procedure)
- presence of metallic implants
- renal function
- allergy to iodinated contrast agents
- heart rhythm

- (cardiac) medication (interaction with adenosine, preparation before adenosine PET, rhythm control during CCTA)
- contra indications for beta-blocker use
- pulmonary function including presence of COPD/asthma
- clinical instability (recent myocardial infarction, decompensated heart failure, hypotension)
- informed consent

6. Radiopharmaceutical

Tracer:	$H_2{}^{15}O$
Activity:	370 MBq (for PET detection in 3 dimensional mode) (dose depends upon characteristics of PET imaging system, above mentioned dose is for 3D mode)
Administration:	Intravenous injection, bolus

Alternatively:

Tracer:	^{13}N-ammonia
Activity:	370-925 MBq (dose depends upon characteristics of PET system, e.g. 2D-3 D mode, crystal)
Administration:	Intravenous injection, bolus or <30 sec of infusion

7. Radiation safety

Pregnancy is a contraindication for cardiac PET/CT procedure

Lactation:

Due to the short half time of ^{15}O /^{13}N-ammonia only a short interruption of lactation is required

Radiation exposure:

$H_2{}^{15}O$: 0,00093 mSv/MBQ

^{13}N-ammonia: 0,0034 mSv/MBq

8. Patient preparation/essentials for procedure

- Refrain from intake of products containing caffeine or xanthine 24 h prior to the scan. This includes beverages such as cola, coffee, tea, energy drinks, foods such as chocolate and medication including anaelgesia containing caffeine.
- Dipyridamol/ Persantin should be stopped 24 h prior to adenosine infusion.
- Cardiac medication which may interfere with the stress test (eg adenosine) should be stopped termporarily. The decision to interrupt cardiac medication should be left to the referring physician. Interruption should ideally be five pharmacological half-lives of relevant drug. This applies for nitrates, but may also apply for beta-blockers and calcium antagonists.
- Severe COPD : consider an alternative stress test.
- The patient should be haemodynamically stable for >48 h prior to the stress test.
- Additional preparation: ECG monitoring, blood pressure monitoring

9. Acquisition and processing

Rest/ stress myocardial $H_2{}^{15}O$ -PET/CT imaging protocol:

- Scout CT for patient positioning

- Two min after starting the intravenous adenosine infusion 140 µg. kg^{-1}. min^{-1}: 370 MBq of $H_2{}^{15}O$ injection as a 5 mL (0,8 $ml.s^{-1}$) bolus, immediately followed by a 35 ml saline flush (2 ml. s^{-1}).

A 6-min PET scan starts simultaneously with the administration of $H_2{}^{15}O$.
This dynamic scan sequence is immediately followed by a respiration-averaged low dose CT scan (LD-CT) to correct for attenuation (55 mAs; rotation time, 1,5 sec; pitch, 0,825; collimation, 16 · 0,625; acquiring 20 cm in 37 sec) during normal breathing.
The adenosine infusion is terminated after the LD-CT.
After an interval of 10 min, to allow for decay of radioactivity and washout of adenosine, an identical rest PET sequence can be performed under resting conditions. There is evidence supporting stress MBF only protocols, therefore the rest MBF PET study is optional.
Image reconstruction: 3D row action maximum likelihood algorithm of 22 frames (1x10, 8x5, x 10,x15, 3x20, 2x30, and 2x60 seconds), including all appropriate corrections.
Parametric MBF images are generated and quantitative analysis can be performed using specifically developed software, Cardiac VUer. Other software packages such as Carimas are available, and yield comparable quantitative results. MBF is expressed in mL· min^{-1} ·g^{-1} of perfusable myocardium and is analysed according to the 17-segment model of the American Heart Association (AHA). Subsequently, MBF is calculated for each of the three vascular territories (right coronary artery [RCA], left anterior descending artery [LAD], and circumflex artery [CX]). The coronary flow reserve (CFR) is defined as the ratio between stress (hyperaemic) and rest (baseline) MBF.

10. Interpretation

The image analysis is performed on both global left ventricular uptake and on a per-vessel basis.
Additionally, a semi-quantitative approach can be used. Myocardial perfusion PET images are divided into 17 segments (AHA model), and each segment is scored using a 5 point scale ranging from 0 (normal perfusion), 1 (mildly reduced perfusion), 2 (moderately reduced perfusion), 3 (severely reduced perfusion), to 4 (absent perfusion). This yields a summed perfusion score for both stress and rest myocardial perfusion images.
After gated acquisition, LV parameters including LV volumes and EF can be used for the overall interpretation.
Quantitative analysis adds information to static uptake image grading. Reported thresholds of what should be considered pathologically decreased stress MBF or CFR are not consistent. Hence, different thresholds should be used for the different PET tracers. The optimal cut-off value for detecting flow-limiting stenosis of coronary arteries by means of $H_2{}^{15}O$ PET hyperaemic MBF is ≤ 2,3 ml·min^{-1}·$g^{-1}$and that for CFR is ≤ 2,5.
In addition, hyperaemic MBF assessment seems to outperform CFR in the diagnosis of obstructive CAD, enabling stress only PET protocols offering a further reduction of PET imaging time.

The hybrid cardiac PET/CT imaging results generally categorise patients into one of four groups:

1. patients with a normal CCTA and normal MBF/CFR, confirming normal coronary circulation.

2. patients with a normal CCTA combined with decreased MBF and/or CRF, indicating coronary microvascular dysfunction
3. patients with an abnormal CCTA and decreased MBF/CFR , indicating vessels with significant stenosis of the coronary arteries.
4. patients with an abnormal CCTA and normal MBF, indicating vessel(s) with non-significant stenosis of coronary arteries.

11. Report

Patient-specific information

- Relevant history, current medication
- Indication for the study
- Type of study (radiopharmaceuticals, acquisition protocol, type of metabolic preparation), haemodynamics and ECG
- Image description (visual, semi-quantitative, quantitative evaluation)
- Quantitative data, including rest MBF, stress MBF, Coronary Flow Reserve, preferably for the three coronary territories (LAD, RCA and CX)
- For hybrid PET/CCTA: correlation between MBF and the main findings of the CCTA (e.g. location of significant coronary obstructive disease and downstream MBF)
- For gated acquisition: LV volumes, EF and wall motion abnormalities
- Conclusion

12. Literature

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weigeringsgrond 10.2.e.

Doc.3

Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport

Artsenverklaring

bestemd om te overleggen aan de fabrikant, groothandelaar of apotheekhoudende voor het afleveren van een geneesmiddel waarvoor geen vergunning voor het in de handel brengen in Nederland is verleend.

Deze verklaring is tot één jaar na dagtekening geldig.

Ondergetekende,

Naam en voorletter(s) arts [redacted]

Specialisme, indien van | Nucleair Geneeskundige

BIG registratienummer arts [redacted]

Werkadres [redacted]

Postcode [redacted] Plaats [redacted]

Telefoonnummer [redacted]

Verklaart hierbij

a) dat zijn/haar patiënt(e),

Codenummer [redacted],

lijdende aan

myocardiale perfusie stoornissen,

niet adequaat kan worden behandeld met in Nederland in de handel toegelaten geneesmiddelen en hij/zij
derhalve voor de behandeling van zijn/haar patiënt(en) wenst te beschikken over het geneesmiddel

Naam geneesmiddel en | 13N-NH3 per spuit.

b) dat hij/zij zich ervan bewust is dat voor het af te leveren geneesmiddel geen vergunning voor het in de handel brengen in Nederland is verleend, en derhalve in Nederland niet is getoetst aan criteria betreffende werkzaamheid, schadelijkheid en deugdelijkheid zoals gesteld in de Geneesmiddelenwet en dat hij/zij zijn/haar patiënt(en) of diens wettelijke vertegenwoordiger nadrukkelijk daarop heeft gewezen.
c) dat hij/zij de volle verantwoordelijkheid draagt en het risico aanvaardt voor de behandeling van zijn/haar patiënt(en) met dit geneesmiddel.
d) dat hij/zij alle hem/haar bekend geworden ziekteverschijnselen die ontstaan tijdens de behandeling en waarbij het vermoeden bestaat dat het geneesmiddel de oorzaak is, zal melden aan de Inspectie voor de Gezondheidszorg; dat hij/zij dit op geanonimiseerde wijze zal melden, zodanig dat de privacy van de betrokken patiënt zal zijn gewaarborgd.

Plaats
[redacted]

Handtekening en datum [redacted]

Dag Maand Jaar
22-02-17

Doc. 4.

weigeringsgrond 10.2.e.

Betreft aanvrage afleveren van ^{13}N-Ammonia

Farmacovigilantieverklaring

Voor ongeregistreerde geneesmiddelen die op artsenverklaring worden geleverd

Na ondertekening deze verklaring toesturen aan Inspectie voor de Gezondheidszorg (IGZ)
Per post: Meldpunt IGZ Postbus 2680, 3500 GR Utrecht
Per fax: 088 - 1205001
Per e-mail (als *.pdf bestand): meldpunt@igz.nl

Aan belanghebbenden

Alle individuele rapporten inzake bijwerkingen (adverse events) en alle andere veiligheidsinformatie verkregen bij de behandeling van patiënten met geneesmiddelen zonder handelsvergunning (via de zgn. "named patient procdure" conform Art. 3.17 van de Regeling geneesmiddelen behorend bij de Nederlandse Geneesmiddelenwet) zullen worden verzameld en geëvalueerd als beschreven in de vigerende Standard Operating Procedure (SOP) voor afhandelen van bijwerkingen van **BAGGERMAN FARMA CONSULT B.V.** en in overeenstemming met andere van toepassing zijnde wetgeving.
De SOP is beschikbaar op aanvraag.

Datum: 24/02/2017
Plaats: Alkmaar
Naam en functie: [redacted] Apotheker [redacted]
Handtekening: [redacted]

FDA

Drugs

Medical and Statistical Review of N-13 Ammonia Positron Emission Tomograpy - August 9, 1999

I. Introduction

This is a primary medical and statistical review of N-13 ammonia radiopharmaceutical used in positron emission tomography (PET) for the indication of assessing myocardial blood perfusion in the evaluation of coronary artery disease (CAD), following separate administration under rest and stress conditions, for patients suspected of having the disease or who have an existing diagnosis of CAD.

Positron emission tomography radiopharmaceuticals have been evaluated and approved by the Food and Drug Administration (FDA) for use as radiopharmaceutical diagnostic agents. Typically, PET radiopharmaceuticals have a short physical half-life and they are manufactured using local cyclotrons or generators. In addition, many of the manufacturers of PET radiopharmaceuticals are located in hospitals and clinics, thus differing from the traditional pharmaceutical and device manufacturers that FDA regulates. In addition, many academic institutions have developed several PET radiopharmaceuticals. FDA has been working with the PET community to develop appropriate criteria and procedures to evaluate PET products for safety and effectiveness. On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA) into law. Section 121 of FDAMA requires FDA to develop procedures under subsections (b) or (j) of section 505 (21 USC 355) for the approval of PET radiopharmaceuticals. FDA believes at this time that it could support the approval of some commonly used PET radiopharmaceuticals under section 505(b)(2) of the act (21 CFR 355(b)(2)).

One of the more commonly used PET radiopharmaceuticals is N-13 ammonia. There have been published reports of N-13 ammonia PET investigations since the 1970s. While the clinical uses for N-13 ammonia PET are diverse in the medical literature, one common theme in N-13 ammonia PET studies is the use of this radiopharmaceutical in the evaluation of myocardial blood flow. Over a flow range of 0 to 300 ml/min per 100 grams, N-13 ammonia tissue concentrations are almost linearly related to flow. At higher flow rates, there is non-linear uptake of N-13 ammonia in myocardium. In addition, hemodynamic and metabolic alterations have little effect on the relationship between flow and net N-13 ammonia extraction. Areas of impaired perfusion appear as defects or lower counts of radioactivity on images. Coupling the scan to a rest and stress component (i.e., exercise or drug-induced hyperemia), similar to rest and stress thallium testing, further assists in assessment of myocardial perfusion under these conditions to aid in the evaluation of CAD.

N-13 ammonia PET has several important features: it allows for a less invasive evaluation of myocardial blood flow; it has high temporal resolution with sampling rates of several seconds, which allow in vivo measurements of regional blood flow; and, using validated radiopharmaceutical kinetic models, quantitative assessment of blood flow is possible. Because of the ability to correct for photon attenuation with PET, it is postulated that PET may be important for patients with equivocal single-photon emission computed tomography (SPECT), e.g., thallium-201 and technetium-99m-based agents, results related to the possibility of photon attenuation, such as patients whose body habitus may cause photon attenuation. All these characteristics of N-13 ammonia PET provide clinicians with the potential of additional diagnostic information to assist them in evaluating patients suspected of having CAD.

The current Agency recommendation for evaluating the diagnostic effectiveness of radiopharmaceuticals for imaging myocardial perfusion in the evaluation of CAD is to conduct studies with an external reference standard of truth, coronary angiography. Coronary angiography involves intravenous iodinated contrast material traversing vessels based in part on osmotic pressure differences and lumen diameter. Vessels with lumen diameters of less than 100 micrometers, however, are not defined by angiography. Coronary angiography reveals

anatomy of arteries and arterioles and degree of stenosis. It is used to identify CAD and its distribution. Thus, N-13 ammonia PET published studies using coronary angiography as a standard of truth, may be evaluated to help determine diagnostic testing performance.

The Agency has approved radiopharmaceuticals to identify regional differences in uptake that are associated with perfusion abnormalities of angiographically-identified stenotic vessels. The location of these perfusion defects is correlated with the location of CAD on angiography. Approved radiopharmaceuticals also identify perfusion abnormalities from smaller vessels (including microperfusion) not identified by angiography. For example, the FDA has approved SPECT radiopharmaceuticals for indications based on their ability to image microperfusion (also called functional perfusion) that is not visible on coronary angiography. These indications for SPECT radiopharmaceuticals include the assessment of myocardial perfusion at rest, exercise, or pharmacologically-induced hyperemia and the evaluation of myocardial function and wall motion.

In the literature, N-13 ammonia PET has been used for these same types of functional myocardial perfusion evaluations. Because N-13 is a radionuclide of a natural constituent of ammonia, as opposed to technetium-labeled products, it is expected to participate in the normal physiological uptake of ammonia. N-13 ammonia is, as mentioned above, highly extractable from the circulation into myocardial cells where it is rapidly metabolized. This property may provide information on microperfusion, in addition to conveying anatomical information (patency or occlusion) about larger vessels. Because myocardial perfusion in coronary artery disease encompasses both anatomical and functional properties, it is important to evaluate N-13 ammonia PET performance with respect to both of these characteristics. For assessing functional aspects, standards other than angiography may be useful, e.g., exercise tolerance, ejection fraction, wall motion, or clinical outcomes, such as cardiac-specific morbidity and mortality.

Of note, the patient population enrolled in N-13 ammonia PET clinical trials, particularly the prospective trials, defined the population in which the diagnostic test's safety and effectiveness were evaluated. No population-based screening trials were published with N-13 ammonia PET and none were reviewed for screening indications.

This review of the N-13 ammonia PET literature serves as the clinical and statistical evaluation of the peer-reviewed scientific literature regarding the effectiveness and safety of N-13 ammonia in PET imaging to assess myocardial perfusion in the evaluation of coronary artery disease, following separate administration under rest and stress conditions, for patients suspected of having the disease or who have an existing diagnosis of CAD. Because of the publicly available safety and effectiveness data documenting the product's use cited in this review, safety and effectiveness requirements of section 505(b)(2) of the act (21 USC 355(b)(2)) and part 314 (21 CFR part 314) for this product and this use may be met by citing the docket number (Docket No.98d0266/ref0001w) of this review.

II. Evaluation of the Effectiveness Data for N-13 Ammonia PET Imaging to Assess Myocardial Perfusion in the Evaluation of Coronary Artery Disease

A. Data Sources

FDA's Center for Drug Evaluation and Research (CDER) conducted a literature search of the recent peer-reviewed, medical journals to evaluate N-13 ammonia PET effectiveness data. Search criteria included: studies published from January 1990 to July 1, 1998 identified as human clinical trials with N-13 ammonia in PET, written in English, found by searching on-line databases of Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts and Embase. Review articles on N-13 ammonia PET imaging were identified using the same criteria in the Cochrane Database for Systemic Reviews and Cochrane Controlled Trials Register. Finally, FDA solicited references from the PET community on N-13 ammonia from any time period published in peer-reviewed journals.

The search generated 76 articles involving clinical trials with N-13 ammonia. Of these, the medical reviewer selected articles which allowed comparison of N-13 ammonia PET myocardial perfusion results to a recognized standard of myocardial perfusion in the evaluation of CAD, such as coronary angiography, or to appropriate comparators, such as rubidium-82 PET, scans using technetium-99m-based agents, or other tests. Other articles were obtained using the reference sections of the primary articles identified in the above searches.

In all, 17 articles are included in this review of effectiveness. Two articles were reviewed as being adequate and well-controlled published studies, 3 were reviewed as controlled studies that were supportive, 9 were reviewed as other published studies that had supporting information, and 3 served as references for a modeling standard that quantified myocardial blood flow. The articles are listed in chronological order under subheadings. Since no studies with pediatrics patients were found, safety and effectiveness in the pediatric population is not addressed by this review.

B. Published Literature

1. Well-controlled and adequate published clinical trials are described below. These published trials allowed FDA to assess the effectiveness of N-13 ammonia PET for myocardial perfusion in the evaluation of CAD by meeting the following criteria: there was comparison between N-13 ammonia PET and an accepted "truth" standard of coronary perfusion or stenosis imaging, coronary angiography; the study population was prospectively enrolled; the entry criteria defined the target clinical population in which N-13 ammonia PET was intended to be used; there were clearly defined endpoints; detailed data on findings were presented; and there were procedures to minimize interpretation bias, such as masking (also referred to as blinding) and randomization, when flow measurement was not performed quantitatively. The first article, Gould (1986), is the initial report of findings and the second article, Demer (1989), is the comprehensive report that includes data from the first study.

a. Gould LK, Goldstein RA, Mullani NA, Kirkeeide RL, Wong WH, Tewson TJ, Berridge MS, Bolomey LA, Hartz RK, Smalling RW, Fuentes F, Nishikawa A. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. J Am Coll Cardiol 1986;7:775-89.

This study conducted at the University of Texas Medical School determined the clinical feasibility of diagnosing significant coronary artery disease by rubidium-82 PET; however, 23 of the 50 patients studied were tested with N-13 ammonia. PET examinations were performed at rest and after intravenous dipyridamole combined with handgrip stress. Coronary angiography was performed.

Inclusion Criteria: There were 50 patients admitted to the protocol who were undergoing diagnostic coronary angiography for chest pain syndromes, evaluation of myocardial infarction, before and after percutaneous transfemoral coronary angioplasty, or as part of a protocol of quantitative coronary angiography before and after plasmaphoresis for cholesterol control.

Dose: Two IV doses of 10-20 mCi N-13 ammonia or 30-50 mCi rubidium-82.

Schema of Trial: A comparison of patient coronary flow reserve as measured by an automated, digitized coronary angiogram program versus rubidium-82 or N-13 ammonia PET perfusion imaging.

Image Protocol: PET images were either obtained before or after cardiac angiography, but were not randomized. The selection of rubidium-82 or N-13 ammonia was determined by availability of the generator. When rubidium was unavailable, N-13 ammonia was used. All PET images were interpreted visually by two observers masked as to the clinical status and angiographic results of the patient. All images were read masked three times in a procedure in which each reading session of all studies utilized one of three different presentation formats: gray scale, tricolor, or isocount color format. For the isocount color format, which had the best correlation results, the composite presentation of all nine heart slice images was interpreted in toto for the entire heart on the rest and then stress studies. Slice-by-slice comparisons were not relied on because of the problem of translation of patient positions. The sessions were separated by 1 to 2 weeks. There was no statement on how dispute resolution was handled. There was no mention of inter-reader variability. Coronary angiograms were analyzed using cine x-ray frames that were digitized using a computer program. The program was automated to identify stenoses and measure stenosis dimensions. From these dimensions, coronary flow reserve (CFR) was calculated. There was no mention of the time interval between PET and angiography examinations.

Primary Endpoints: Coronary artery stenosis was based on angiography and defined by using a scale of 0 to 5, with 0 being no flow and 5 being normal. Significant CAD was determined to be a CFR of less than 3.0 on angiography. The investigators discussed their rationale for selection

of 3.0 CFR. This endpoint was chosen prospectively. PET detected perfusion defects were defined by the isocount color format and the continuum of changing count densities as reflected in hue gradation of each color corresponding to steps of 3% of maximal counts upon evaluation of the rest and stress-hand grip images. All nine slices of heart images had ranges of density counts scaled in 33 steps with black for the lowest counts (<20% of maximum counts), to blue (20-35% of maximum counts), to green (35-50% of maximum counts), to yellow (50-68% of maximum counts), to red (68-85% of maximum counts), to white (85-100% of maximum counts). Reduction in coronary perfusion is manifested as colors indicating the percentage reduction of maximum counts. Although not specifically stated, it appears from the study's statement of, "...a large anterior wall defect in which counts are 50% below the normal areas, indicating at least a 50% reduction in coronary flow reserve," that percent count reduction is correlated to CFR.

Results: Fifty patients were studied, but 6 patients were excluded from analyses because of technical errors of positioning and computer errors. These 6 patients were imaged as the first subjects and the investigators learned from these initial experiences. There is no mention of sex or age distribution. Data from rubidium-82 and N-13 ammonia studies were pooled. Twenty-two patients had CAD with an angiographically determined CFR of less than 3.0 (significant CAD); 9 were without CAD on catheterization; and 13 had CAD with CFR of 3 or greater (mild disease). PET sensitivity of identifying significant CAD (less than 3.0 CFR) was 95% (21 out of 22), specificity (patients without CAD) was 100% (9 out of 9), however, identifying insignificant CAD (CFR of 3 or greater) was 31% (4 out of 13) for PET. This means only 31% of the patients with milder disease were identified by PET; 69% of patients with milder disease were missed. Sensitivity for significant left coronary artery system disease was 89% (16 of 18) and for right coronary artery system disease it was 100% (9 of 9).

Rubidium and N-13 ammonia images were compared qualitatively. The study states that the quality of images using the two radiopharmaceuticals were comparable, although "the quality of images is a function of the dose given to compensate for the greater decay of rubidium-82 up to the time of data acquisition." In addition, N-13 ammonia images had more activity in the liver than rubidium-82.

The study also presents results of angiography compared to all three formats of image presentation (isocount, gray scale, and tricolor format). The isocount color format had the most favorable agreement with angiography results. The other formats had more problems with interpreting intensity of gray or uni-color scale, image plane displacement with slice by slice comparisons, and, thus, greater variability of interpretation among readers.

Safety Issues: Side effects of intravenous dipyridamole were presented in a table: headache and flushing occurred in 46% and 52% of patients respectively, followed by 24% with chest pain, 13% requiring aminophylline, and 9% have ST segment changes. Nausea, dizziness and PVCs/SVTs were reported less than 10% of the time. No safety issues associated with administration of N-13 ammonia are mentioned.

Commentary: The study has many strengths.

The study encompassed the proper study population for PET imaging: those who had indications of possible CAD and were undergoing cardiac catheterization. This appears to be a prospective collection of patients. There were subjects with normal coronary anatomy included in the selection. Although small in sample size, the study had the appropriate enrollment criteria to encompass a board spectrum of the disease, patients with possible CAD.

Another strength is that PET imaging is compared to an accepted standard, cardiac angiography. Furthermore, the interpreting physicians were masked and read images of the same patient three times. This procedure permits determination of intra-observer variability. The investigators also addressed the problems of comparing PET perfusion images to single geometric measurements of stenosis severity obtained during angiography by the calculation of CFR on angiograms. In 1986 when the study was published, CFR could not be calculated from PET imaging. The software to calculate CFR by quantifying and validating activity within a three-dimensional reconstruction of cardiac radiopharmaceutical distribution was under development.

Significant CAD was defined prospectively as a CFR from angiography of less than 3.0 and then this was applied to sensitivity and specificity of rest-stress PET imaging. This specific statement in the study eliminates concerns about data manipulations to fit hypotheses. PET sensitivity of identifying significant CAD (less than 3.0 CFR) was 95% (21 out of 22), specificity (patients

without CAD) was 100% (9 out of 9), however, identifying insignificant CAD (CFR of 3 or greater) was 31% (4 out of 13) for PET.

Weakness in the study centered on the lack of information on inter-reader variability, if images were read independently, frequency of disagreement of PET interpretations, and dispute resolution. Results were not stratified by radiopharmaceutical (rubidium versus N-13 ammonia), as well. However, the study did mention, "There was no difference in sensitivity and specificity between the two tracers in this small number of patients." This implies that data was analyzed to support this statement, but, as is often the case with peer-reviewed literature, was not published. The study is limited also by its small number of subjects. It was reviewed in the context of being a preliminary report to the more comprehensive study by Demer, which follows. Finally, the study did not clearly state the relationship between isocounts and CFR as measured by angiography. While rationale for the selection of 3.0 CFR for significant CAD is discussed, there is lack of discussion on what defined significant CAD for PET isocount images. Inference is made from reading captions on figures that the percent of maximum counts is directly correlated to the same percent reduction in CFR. While these data and definitions often exist and are documented in studies, they may be absent from the final published study.

Overall, this study is well-designed and has results supporting N-13 ammonia PET as being similar to the already FDA-approved rubidium-82 radiopharmaceutical for assessing coronary perfusion in the evaluation of coronary artery disease, following separate administration under rest and stress conditions, in patients suspected of having the disease.

b. Demer LL, Gould LK, Goldstein RA, Kirkeeide RL, Mullani NA, Smalling RW, Nishikawa A, Merhige ME. Assessment of coronary artery disease severity by PET: comparison with quantitative arteriography in 193 patients. Circulation 1989;79:825-35.

This study from the University of Texas Medical School assessed the accuracy of N-13 ammonia PET rest and stress (dipyridamole) tests in evaluating CAD compared to coronary angiography in 193 patients (82 received rubidium-82 and 111 received N-13 ammonia). It is a follow up to the preliminary Gould study and includes the patients in the Gould article. It makes advances over other studies by assessing CAD with a continuous scale to cover the range of disease severity rather than the binary classification and using direct correlation rather than sensitivity-specificity analysis. This study also enrolled larger numbers of patients.

Inclusion Criteria: All patients were undergoing cardiac catheterization for: chest pain syndromes, myocardial infarction, abnormal stress tests, coronary angioplasty, thrombolytic therapy or acute infarction, evaluation before renal transplant, before or after cholesterol lowering programs, or as part of screening feasibility studies. Patients either received rubidium-82 or N-13 ammonia. There were 143 men and 50 women studied. Sixty-six had a previous diagnosis of myocardial infarction.

Dose: Reference was made to previous articles, including the published study in II(B)(1)(a) where the doses are stated as two IV doses of 10-20 mCi N-13 ammonia or 30-50 mCi rubidium-82.

Schema of Trial: A comparison of patient stenosis flow reserve (SFR) as measured by an automated, digitized coronary angiogram program versus rubidium-82 or N-13 ammonia PET perfusion imaging. Scoring of both diagnostic tests was on a continuous scale.

Image Protocol: PET images were either obtained before or after cardiac angiography. There is no mention of randomization. The selection of rubidium-82 or N-13 ammonia was determined by availability of the generator. When rubidium was unavailable, N-13 ammonia was used. All PET images were interpreted visually by two observers masked as to the clinical status and angiographic results of the patient. All images were read independently and they were displayed using the isocount color format. Rest and dipyridamole stress images were displayed either side-by-side or superimposed with adjustable color scales. Seven regions of each cardiac image (anterior, apical, anteroseptal, posterseptal, anterolateral, posterolateral, and inferior walls) were evaluated. PET detected perfusion defects were defined by the color format and the continuum of changing count densities as reflected in hue gradation of each of five primary colors corresponding to steps of 3% of maximal counts upon evaluation of the rest and stress-hand grip images. Perfusion defects were defined as regions of subjectively-interpreted lower counts in at least two contiguous slices compared to the remainder of the heart. Perfusion defects were graded on a 0 to 5 scale: 0 is normal, 1 is possible, 2 is probable, 3 is mild, 4 is moderate, and 5 is severe. One score is assigned to each region and each step of the scale is

one primary color step. The average of the two readings was taken for each region. Scores were assigned by each reader and then averaged to define a PET defect severity score. Interobserver differences in PET scan interpretation were defined, tracked, and analyzed. A dispute resolution protocol was defined and images with qualitatively different interpretations were reread independently (8 cases) and either had agreement (2 cases) or were divergent and had scores averaged (6 cases).

Coronary angiograms were analyzed using cine x-ray frames that were digitized using a computer program that automatically detects vessel borders. Absolute and relative stenosis dimensions were measured. From these dimensions, stenosis flow reserve was calculated. SFR is defined as the intersection of flow at maximum coronary vasodilation relative to rest flow, under standardized hemodynamic conditions. SFR scores ranged from 0 (total occlusion) to 5 (normal). There was no mention of the time interval between PET and angiography examinations.

Primary Endpoints: Scores of PET defect severity on N-13 ammonia PET imaging (0 to 5; 0 is normal, 1 is possible, 2 is probable, 3 is mild, 4 is moderate, and 5 is severe) and scores of SFR (0 to 5; 0 being total occlusion; <3 is significant CAD; 3<SFR<4 is mild CAD, and SFR >4 is normal coronary artery) for patients and for regions of the heart.

Results: There were 115 patients with significant CAD (SFR <3), 37 patients with mild CAD (3<SFR<4), and 41 patients with normal coronaries (SFR>4). There is no mention of age or sex distribution of the subjects. Data for N-13 ammonia and rubidium-82 studies are pooled. With increasingly severe impairment of stenosis flow reserve, subjective PET defect severity scores increased. Despite wide scatter SFR scores per PET scores, a PET score of 2 or more was highly predictive of significant CAD (SFR<3). The Spearman correlation coefficient was 0.77 +0.06 for patient scores of the most severe PET defect correlated with the SFR of the patient's most severe stenosis (n=174 patients). Nineteen patients were excluded from this analysis "because they had undergone revascularization during acute infarction causing residual stenosis severity that would not be comparable to the severity of the fixed perfusion defect."

The study did supply the following information on rubidium-82 and N-13 ammonia performance: "Images obtained with rubidium-82 and N-13 ammonia tracers were qualitatively similar. The two false positive cases included one N-13 ammonia and one rubidium-82 image. Of the 7 false negative scans, five were N-13 ammonia scans and 2 were rubidium-82. Thus, 79 of 82 rubidium images and 105 of 111 ammonia images were consistent with the arteriographic results. These ratios were not significantly different (p=0.73)." Unfortunately, the total of 193 cases includes cases that were excluded from the analysis. The study's analysis only included 174 cases. The numbers provided above do not aid in the calculation of a sensitivity or specificity for N-13 ammonia, but do provide information that suggests the comparability of the N-13 ammonia and rubidium-82, an FDA-approved radiopharmaceutical.

The authors provided graphical representation that do permit an estimate of N-13 ammonia PET sensitivity and specificity using data from the plot of mean stenosis flow reserve score (5-0) versus subjective PET defect severity score (0-5). See Appendix A: Figure 3. This data shows considerable scatter SFR scores of each PET score. By visually interpreting Figure 3's lower plot, there are a total of 96 patients with significant CAD (SFR <3) and 78 patients with SFR >3. PET scores reveal 106 patients that are CAD-positive (PET defect severity score >2) and 68 patients are PET CAD-negative (PET defect severity score <2). If one attributes 2 out of the 4 patients with a PET score of 1 and a SFR of <3 (significant CAD) from the plot as being PET false positive results, we can calculate the remaining cells of a 2 x 2 table. The 4 patients with PET score of 1 had SFR values ranging from greater than 2.2 to about 3.8 and the exact number of patients with a SFR <3 (PET false negatives) is not stated. Thus, as an arbitrary approach, the value of 2 out of 4 patients was assigned as it represented about the same spatial percentage of error bar below a SFR of 3.

Significant CAD per Angiography in Patients

(n=174 patients)

Diseased Non-diseased

(SFR <3) (SFR > 3)

totals:

PET Score >2 94 12 106

CAD per PET

in patients PET Score <2 2 66 68

totals: 96 78

Sensitivity=98%

(95% Confidence interval 92.1-99.7%)

Specificity=85%

(95% Confidence interval 74.7-91.7%)

These numbers, however, seem to differ from the data quoted for the total 193 patients having a total of 2 false positive and 7 false negative cases for N-13 ammonia and rubidium-82 combined.

For each of the 243 stenoses, PET defect severity score correlated with the SFR of the corresponding artery with a Spearman coefficient of 0.63 +0.08. There were variations in this relationship that were attributed to subjective scoring of PET defects, anatomic variations, and other reasons.

By visually interpreting the accompanying plot of stenosis flow reserve score in reverse (5-0) versus the subjective PET defect severity score (0-5), there are a total of 135 vessels with significant CAD (SFR <3) and 108 vessels with SFR >3. PET scores reveal 161 vessels that are positive (PET score >2) and 82 are PET negative (PET score <2). If one attributes 2 out of the 5 patients with a PET score of 1 and a SFR of <3 (significant CAD) from the plot as being PET false positive results, we can calculate the remaining cells of a 2 x 2 table. The 5 patients with a PET score of 1 had SFR values ranging from greater than 2.5 to about 4.8 and the exact number of patients with a SFR <3 is not stated. Thus, as an arbitrary approach, the value of 2 out of 5 patients was assigned as it represented about the same spatial percentage of the error bar below 3.0 SFR.

Significant CAD per Angiography in Vessels (n=243 vessels)

Diseased Non-diseased

(SFR <3) (SFR > 3)

totals:

PET Score >2 133 28 161

CAD per PET

in vessels PET Score <2 2 80 82

totals: 135 108

Sensitivity=99%

(95% Confidence interval 94.9-99.9%)

Specificity=74%

(95% Confidence interval 64.5-81.7%)

Readers had agreement on whether the most severe PET defect was less than or more than a score of 2 for 89% of patients. Overall agreement data for all observations were presented for both rest and stress scans, including the amount of disagreement. In 82% of rest scans and 83% of stress scans the two numeric scores were in agreement, as defined by a difference of no more than 2 in PET score.

Safety Issues: No safety issues were reported.

Commentary: This study expands on the earlier study by the same authors with a larger number of patients. Many of the strengths of the earlier study are also present here: use of coronary angiography as the accepted standard, the entry criteria encompasses the appropriate population for which PET may be indicated (those patients with suspected CAD), and the use of a quantitative program to measure angiographic results. Moreover, this study addresses

weakness of the previous study by reporting detailed information on readers' performances and variability of interpretation, and by analyzing results in the presence of variability. SFR is proposed as a better indicator of coronary perfusion in angiographic images compared to percent stenosis. Dispute resolution is described fully. The authors still acknowledge that quantitative measurements of PET perfusion are preferable, but at the time of the 1989 study, it was not validated. N-13 ammonia and rubidium-82 data are pooled. The authors had stated that sensitivity and specificity were comparable for both agents, although the analyses were not published. While information is provided in the text about how N-13 ammonia PET performed, as opposed to rubidium-82, this information does not allow estimates of N-13 ammonia PET performance and appears to differ from information in Figure 3.

The study contained enough data to attempt to create 2 x 2 tables to estimate sensitivity and specificity based on patients and vessels, using the authors' cut off points for a positive and negative PET test and the authors' definitions of significant CAD and non-significant CAD. Because no data for the tables' cells were specified, an approach was outlined above that allowed data to be generated based on a the published graphical information.

This study further supports the ability of N-13 ammonia PET

to assess myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, for patients suspected of having the disease.

2. Other Controlled Published Studies

The following 3 studies of N-13 ammonia PET provided additional information concerning the test's ability to assess myocardial perfusion in the evaluation of CAD for patients suspected of having the disease. The study hypotheses were, however, somewhat variable. The patient populations were selected retrospectively based on previous angiographic data. Normal volunteers were selected to represent CAD-free patients. While there was direct comparison of PET results to other standards, including angiography, or rubidium-82 PET, scans using technetium-99m-based agents, or other tests, this comparison was at times not the primary endpoint. Enough detailed data, however, were presented to allow assessment of N-13 ammonia PET effectiveness in myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions.

a. Schelbert HR, Wisenberg G, Phelps ME, Gould KL, Henze E, Hoffman EJ, Gomes A, Kuhl DE. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. Am J Cardiol. 1982;49:1197-1207.

This study from the University of California, Los Angeles, compared the sensitivity of N-13 ammonia PET in detecting coronary artery disease in normal volunteers and patients with angiographically documented coronary artery disease (CAD) using rest and stress (dipyridamole) testing.

Inclusion Criteria: Thirty-two patients with CAD, who had all undergone routine coronary angiography prior to enrollment, were chosen to participate. Twenty-two were men and 10 were women. The ages ranged from 31 to 68 years with a mean of 53.1 years. In the 13 normal volunteers (their ages ranged from 18 to 44 years with a mean of 25.2 years, all male), there was no clinical or EKG evidence of CAD. Eleven patients with CAD underwent thallium-201 exercise stress testing within an average of 15.8 days (range 1-42) of N-13 ammonia study.

Dose: 0.22 (+ 0.09)mCi/kg N-13 ammonia injected IV per dose given in two doses.

Schema of Trial: Patients with CAD on angiography and normal volunteer controls were randomized in sequence to undergo N-13 ammonia PET resting and stress testing using dipyridamole. Imaging results were compared to angiographic results. Normal controls did not undergo angiography. A subset of CAD patients, eleven, underwent exercise-stress thallium-201 testing for comparison with angiography and PET.

Image Protocol: Patients and controls were randomly sequenced to undergo PET. There were two independent observers for PET readings who were masked to subject's clinical status or symptoms. A study was considered abnormal if a regional defect in myocardial N-13 activity was observed in the hyperemic (post-dipyridamole) image that either was not present or considerably larger than that in the control image. Observer agreement was excellent. Four patient studies that had disagreement over numbers of vessels involved were jointly reviewed

and agreement reached by consensus. Eleven patients also underwent thallium-201 exercise stress testing within an average of 15.8 days. Coronary angiograms were done within an average of 11 weeks in advance of the PET studies.

Primary Endpoints: The appearance of uniformity (normal) or reduction of N-13 activity (abnormal) distributed in the myocardium at various anatomically correlated regions of the heart's vasculature system through angiographically defined stenoses. Hemodynamically significant stenosis was defined as 50 percent or greater (diseased vessel). Thallium-210 studies were defined as positive for stress-induced ischemia if the immediate post-exercise images showed regional reductions in myocardial thallium-201 activity that were either completely or partially resolved on the delayed images.

Results: In the 13 normal volunteers, N-13 activity was uniform at rest and during hyperemia, whereas 31 out of 32 CAD patients had regional defects on the hyperemic images not present during rest. No false positive images were obtained on the normal volunteers. The data can be represented in the following table:

Angiographically- Normal

defined patients w/CAD Volunteers

(>50% stenosis)

Patients with PET 31 0

perfusion defect

Patients without PET 1 13

perfusion defect

Sensitivity is about 97% and specificity is assumed to be 100%, if all normals were, in fact, disease-free.

Of all 58 stenoses identified on coronary angiography, 52 (90 percent) were correctly identified by N-13 ammonia PET. Of the 19 angiographically-identified, stenosed coronary arteries in the subgroup who underwent exercise thallium-201 planar imaging, 11 (58 percent) were correctly identified with thallium-201 and 17 (89 percent) with N-13 ammonia PET.

Safety Issues: The article mentioned the purity of N-13 ammonia was greater than 99 percent. There were 12 patients with CAD (37.5 percent) with chest discomfort or pain on infusion of dipyridamole and 9 of these patients received aminophylline IV. No adverse events were reported with N-13 ammonia infusion.

Commentary: This study used both coronary angiograms and exercise stress thallium testing to compare the diagnostic performance of N-13 ammonia PET. The study provided detailed data on patient and vessel comparative results. The study also included normal controls, although these patients did not undergo coronary angiography. While the study encompassed small numbers, the PET results were for the most part consistent among the two observers and highly correlated with angiographic data of patients with CAD (31 out of 32 (97%) CAD patients were correctly identified by PET).

Although the mean time difference from angiography to PET was 11 weeks, all CAD patients were in symptomatically stable condition with no evidence of clinical progression of their disease.

The design was a comparative trial with angiography as the standard of truth, and the study assumed normals did not have CAD. This means that CAD patients were defined by their previous angiography results as having stenoses and subsequent PET results were compared to angiography results to assess presence of perfusion abnormalities correlating with stenoses. As an initial study, investigators must first assess a new technology on a pre-defined population where "truth" is known, and, for specificity, where truth is assumed. The study does not allow us to calculate the true specificity of PET, only the estimated specificity based on an assumed truth. Only a subset of 11 patients with CAD underwent stress-thallium testing. These thallium rests were compared to both PET and angiographic data for patients and for individual vessels to assess concordance of stenoses and perfusion defects. This comparative study obtains important information on how the test performs relative to thallium and then how both ultimately compared to the accepted truth standard, angiography. The weakness of this

approach is it assumes angiography is, in fact, the ultimate truth. As stated earlier, PET and SPECT radiopharmaceuticals and angiography may measure different aspects of coronary anatomy. N-13 ammonia is a functional examination of microperfusion. N-13 ammonia exchanges across the capillary and cellular membranes via diffusion, while angiography is a structural assessment of patency. Correlation of results between PET perfusion defects and angiographic stenoses is acceptable, although it may be intrinsically difficult.

A weakness of the study is retrospectively selected study populations do not test how the test will be used in practice (along with or in lieu of coronary angiography) nor do they provide information on how the test performs in the target population. The sample size is also very limited. The study, however, provides information as proof of concept.

Other concerns raised from the study center around entry criteria. Selection criteria for angiograms of CAD were not stated. Selection criteria for the 11 patients who underwent exercise thallium-201 were also not provided. No information on patient refusal or dropouts is provided.

Not having specific entry criteria for patients with CAD can have advantages. There are a wide variety of patients with CAD, from diabetic to hyperlipidemic to hypertensive, and vascular changes from these different conditions may differ. Diabetic vessel disease is primarily a small vessel disease while other processes affect larger vessels. General entry criteria would serve to increase generalizability of the results to a wider patient population. However, no criteria are specifically stated in the study.

The study did not mention if the angiograms and thallium-201 exercise tests were read by the same two observers as the PET studies or the manner and sequence the three tests were read. The study did state that readers were "unaware of the patient's clinical state or symptoms," implying that CAD status was not known. However, there was no mention if images of rest and exercise PET, thallium-201, or coronary angiography images were presented in an unpaired fashion to the readers. Because none of the normal volunteers had angiograms or thallium tests, it is preferable that all tests be read separately and unpaired. Otherwise, it would be easy to determine case and control status, which may bias readers.

This study appears to have a high degree of agreement between the two observers for PET readings. In addition, the protocol specified the exact types of disagreement encountered and how disagreements were handled. The study used resolution by consensus reading, a common, but potentially biased, means to address disagreement.

As with many studies relying on interpretation of visual images, observer performance is important. Concerns for observer performance may be reflected in the subjective and subtle nature of reading PET images based on appearance of degrees of homogeneity. Performance may be highly correlated to experience and skills of each interpreting physician, which could be quite variable. In 1982, when this study was published, PET was extremely limited in its use and experience was not widespread. This published early experience may have raised concerns at that time about reproducibility in the general imaging community, which lacked exposure to the technology. However, it appears that over the next fifteen years, other studies have been published supporting rather consistent performance by interpreting physicians with N-13 ammonia PET.

In summary, this 1982 study was a study comparing PET, thallium, and angiography readings in retrospectivly selected patients with known CAD and normal volunteers. The strength of the study lies in its consistent results across two independent readers, despite having a subjective, dichotomous endpoint: normal or abnormal homogeneity of radiopharmaceutical activity. The correlation between PET results and angiography with respect to patients and vessels identified as diseased is reproduced from Gould (1986) and Demer (1989). N-13 ammonia PET had 97% sensitivity (31 of 32 patients) for identifying patients with angiographic CAD. The study supports the utility of N-13 ammonia PET for assessing myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions.

b. Di Carli M, Sherman T, Khanna S, Davidson M, Rokhsar S, Hawkins R, Phelps M, Schelbert H, Maddahi J. Myocardial viability in asynergic regions subtended by occluded coronary arteries: Relation to the status of collateral flow in patients with chronic coronary artery disease. J Am

Coll Cardiol 1994; 23:860-68.

This study was conducted at the University of California Los Angeles School of Medicine. This study determined whether angiographically visualized collateral vessels in patients with chronic CAD and left ventricular dysfunction imply the presence of viable myocardium in regions with wall motion defects subtended by completely occluded coronary arteries as assessed with rest N-13 ammonia and fluorine-18 deoxyglucose (18-FDG) PET. Viability is defined in this study as the characterization of myocardial metabolism with PET fluorine-18 deoxyglucose. The purpose was to provide data on the relationship between angiographic collateral flow, myocardial wall motion abnormalities, and myocardial viability as defined by preserved metabolism of 18-FDG.

CAD patients considered for revascularization often have severe wall motion abnormalities. This myocardial dysfunction may respond variably to revascularization. The differentiation of reversible from irreversible myocardial dysfunction is useful in decision-making about revascularization for each patient candidate, and this is not sufficiently achieved by use of angiographic data alone. Hypothetically, this differentiation permits prediction of functional outcome after revascularization. Areas of reversible dysfunction may be at high risk for further ischemic events on medical therapy. Because angiography only visualizes collateral flow in vessels greater than 100 micrometers in diameter, N-13 ammonia perfusion was hypothesized as being able to assess microperfusion in areas of wall motion dysfunction subtended by completely occluded coronary arteries.

Inclusion criteria: Forty-two consecutive patients with confirmed CAD on catheterization and left ventricular dysfunction were referred for assessment of myocardial viability defined by the pattern of PET 18-FDG metabolism. The study group consisted of 37 men and 5 women, aged from 34 to 81 years. Thirty-five patients had a history of previous myocardial infarction, 35 patients had symptoms of heart failure, and 17 patients had angina.

Dose: 20 mCi of N-13 ammonia and 10 mCi of 18-FDG injected intravenously.

Schema of trial: Comparisons of the extent of PET viability patterns and the severity of perfusion defects between three groups of angiographic collateral flow grades were performed.

Image Protocol: All patients underwent coronary angiography and contrast left ventriculography before PET imaging. Rest regional myocardial perfusion and glucose metabolism were assessed with N-13 ammonia and 18-FDG imaging, respectively. The N-13 ammonia PET imaging was completed first followed by 18-FDG PET imaging. Two experienced observers who were masked to the PET results assessed independently segmental wall motion from the contrast left ventriculography and collateral flow from the coronary angiograms. Discrepancies between readers were resolved by consensus. PET image myocardial perfusion and glucose uptake were scored separately for each segment by consensus visual analysis of two observers masked to all patient clinical data. The time interval between MI and angiography ranged from 2 months to 14 years. The period between the PET study and coronary angiography ranged from 4 to 70 days.

Primary Endpoints: The PET measures of perfusion and viability patterns were compared to the angiographic collateral flow grade in the myocardial territories with totally occluded major coronary arteries with corresponding myocardial wall motion defect.

The presence and severity of wall motion abnormalities was scored using a 6-point scale from contrast ventriculography. From the angiograms, the presence of collateral vessels to occluded arteries for each image was classified into 3 collateral flow grades: 1 = absent, 2 = minimal, 3 = well developed.

From the PET images, myocardial perfusion (N-13 ammonia) and glucose uptake (18-FDG) were scored separately for each segment using the following 5-point uptake scale: 0 = absence of background, 1 = severe defect, 2 = moderate defect, 3 = mild defect, 4 = normal uptake.

PET viability patterns (match, mismatch, and normal) for each segment were based on comparison of the N-13 ammonia and 18-FDG uptake scores. Segments with perfusion defect (N-13 ammonia score <3) were classified as mismatch when the 18-FDG score was higher than the N-13 ammonia score by at least 1 point. A match was defined as when both the N-13 ammonia and 18-FDG uptake were both severely reduced or absent (score of 0 or 1) or, for a transmural match, both mild to moderately reduced (score 2 or 3). Normal was defined as both PET scores being 4.

The severity of perfusion deficit was assessed quantitatively by calculating the average percent

reduction of relative myocardial N-13 counts below the limits of a normal data base (percent perfusion below normal value) in each region.

Results: There was no significant correlation (p=0.14) between the severity of perfusion deficit seen on N-13 ammonia PET and the collateral grade assessed by angiography. The extent of mismatch was unrelated to either the presence or the magnitude of collateral vessels. Myocardial viability defined by 18-FDG uptake was present in severely hypokinetic regions 82% of the time. Viability by 18-FDG uptake was present in 49% of akinetic-dyskinetic regions. Of the 64 regions with angiographic collateral vessels, 37 (58%) showed PET mismatch (18-FDG score was higher than the N-13 ammonia perfusion score). In the 14 regions without collateral vessels on angiography, 7 (50%) exhibited PET mismatch. The presence of angiographically visualised collateral vessels was a sensitive (84%) but not specific (21%) marker for viability, defined as 18-FDG metabolism (mismatch or matched presence of both 18-FDG and N-13 ammonia activity).

The study concluded that in patients with chronic coronary artery disease, angiographically visualized collateral vessels to myocardial regions with wall motion defect and subtended by occluded coronary arteries do not always imply the presence of viable myocardium. The study also concluded that PET studies may be a possible aid in assessing patients' myocardial viability for decisions about revascularization.

Safety Issues: No safety issues were reported.

Commentary: By the time this article was written in 1993, N-13 ammonia PET had been used frequently to measure myocardial blood flow. In addition, N-13 ammonia had been coupled with 18-FDG to study the potential viability of myocardial tissue. While this study went beyond assessing myocardial perfusion in the evaluation of CAD with N-13 ammonia PET, this aspect can still be commented upon. In fact, this study has many strengths with respect to myocardial blood flow measurement by N-13 ammonia PET.

One strength was that the standards of coronary angiography and contrast left ventriculography were used to grade collateral vessel supply to those myocardial regions with completely occluded arteries and abnormal wall motion. In this study, the set of readers for the angiogram and ventriculogram were masked to the results of the PET study to decrease bias. Another strength was that PET myocardium perfusion values were quantitatively assessed by a machine-dependent program. These results were then correlated to describe the relationship between collateral grade and blood flow value. Finally, the study population, 42 consecutive patients with CAD, was appropriate for the demonstrating the test's performance in the target population.

The study demonstrated that the presence of angiographic collateral blood flow to akinetic myocardium may not predict living myocardial tissue and the absence of collateral flow may not predict non-living myocardial tissue. In 58% of cases where angiographic collateral vessels were present, PET demonstrated reduced N-13 ammonia perfusion with 18-FDG metabolism (mismatch); in 50% of cases where angiographic collateral blood flow was absent, there was still perfusion, although reduced, with metabolism of 18-FDG. These findings appear to contradict findings of Gould (1986) Demer (1989) and Schelbert (1982), which rely on good correlation between angiographic stenoses and PET. However, this study population was very different: patients had more severe CAD with severe asynergy of the myocardium supplied by the occluded vessel. Moreover, 83% had a history of previous myocardial infarction. It may be that in this patient population, subendocardial and intramural intercoronary vasculature are present, but, per the authors' discussions, are not angiographically demonstrated because these vessels are as small as 20 micrometers in diameter. In addition, the authors state that there may be low pressure gradient between the supplying occluded artery and the collateral vessels preventing angiographic visualization. Thus, the study's results do not necessarily contradict the previously mentioned ones.

A weakness of the study was absence of formal accounting for inter-reader variability for the masked readers of the angiographic images. Instead, the results of the two masked readers were condensed into one response by consensus after the images were rated independently. This method for handling inter-reader variability is not completely informative; it would have been of interest to know how much discrepancy was present and for what regions the discrepancies occurred. Another weakness was the small numbers of subjects studied.

Overall, this study demonstrated that myocardial blood flow measured by N-13 ammonia PET

affords information different from angiography, although complementary. By studying N-13 ammonia PET in this extreme end of the spectrum of coronary artery disease, this study provides useful information on PET performance in this population. There is detailed information on PET image acquisition and analysis. Angiographically visualized collateral vessels (grade 2, minimal, and grade 3, well-developed collaterals) detected PET mismatch (reduced, but present N-13 ammonia perfusion with 18-FDG metabolism) 84% of the time (37 of 44 territories). This data suggests that both angiography and N-13 ammonia PET contribute information on myocardial perfusion in the evaluation of CAD. The study contributed to the FDA assessment of N-13 ammonia PET.

c. Gewirtz H, Fischman AJ, Abraham S, Gilson M, Strauss HW, Alpert NM. Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction. J Am Coll Cardiol 1994; 23:851-59.

This single center study was conducted at Massachusetts General Hospital, Boston, Massachusetts. The study hypothesized that a minimal level of blood flow is required to sustain myocardial viability, below which the myocardial region would consist mostly of scar. This study assessed whether chronically infarcted, nonviable myocardium could be identified by quantitative measurements of regional myocardial blood flow obtained using N-13 ammonia and 18-FDG PET in conjunction with a mathematical model of N-13 ammonia radiopharmaceutical kinetics.

Inclusion criteria: The study group consisted of 26 patients (25 men, 1 woman; from 34 to 74 years of age) with documented chronic myocardial infarction based on historical and ECG evidence of previous MI. Patients were initially referred for a clinically indicated thallium stress test. The referring physician also requested the PET study. Patients who were diabetic, had myocardial infarction <2 months or had cardiac catheterization >14 months before the PET study were excluded from the study group.

All patients had cardiac catheterization and were clinically stable without recent (2 weeks) unstable chest pain. The time between PET scan and previous myocardial infarction ranged from 2 to 192 months. Cardiac catheterization (angiogram) was done within a mean of 5 months for all patients. Eleven patients had had revascularization of the infarct zone. The mean time between revascularization and PET study was 11 months. Cardiac and other medications were continued.

Dose: Approximately 25 mCi of N-13 ammonia, 7.5 mCi of 18-FDG.

Schema of trial: The study proposed to demonstrate that chronic infarct zones with very low flow compared with normally perfused regions of the heart under basal physiologic conditions should be composed largely of scar (non-viable myocardium, defined by 18-FDG PET metabolism).

Image Protocol: PET myocardial perfusion study at rest with N-13 ammonia and myocardial metabolism study with 18-FDG images were acquired. Regional myocardial blood flow and regional 18-FDG uptake were calculated using the same regions. All flow computations were made without knowledge of regional wall motion data. Appropriate segments of the PET images and radionuclide image were matched for comparisons.

For wall motion analysis, contrast biplane left ventriculography was performed in 21 patients, multi-projection radionuclide ventriculogram in 3 patients, and echocardiogram in 2 patients. All ventriculograms were interpreted without knowledge of PET myocardial blood flow measurements by the clinician who performed the cardiac catheterization.

Primary Endpoints: Myocardial viability was evaluated both by analysis of regional wall motion and by objective assessment of the relation between myocardial glucose metabolism and myocardial blood flow. Specific results for regional myocardial blood flow were correlated with descriptions of various states of coronary artery stenosis, and there was myocardial blood flow correlation with the results of metabolic (18-FDG) imaging and with regional wall motion.

There was no mention of how angiograms were evaluated or by whom.

Myocardial regions were designated as normal, border, or infarct zones on the basis of percent of maximum regional myocardial flow via N-13 ammonia PET. All infarct zones corresponded to regions of previous MI as determined by historical and ECG criteria.

Regional myocardial blood flow and 18-FDG uptake were compared to determine if a region had

a mismatch outcome, a presumed surrogate of myocardial viability. A mismatch was defined objectively as a difference between relative 18-FDG uptake and relative flow of >0.34.

Regional wall motion was another indicator of myocardial viability. Segments were classified as: viable if they had normal wall motion or only mild hypokinesia; scar if they had dyskinesia; or either viable, scar, or both if they had severe hypokinesia or akinesia.

Results: In patients with chronic myocardial infarction, normal blood flow (0.81 +0.32 ml/min per g) was greater ($p < 0.02$) than that of border zones (0.59 +0.29 ml/min per g), which also exceed ($p<0.001$) that of infarct zone flow (0.27 +0.17 ml/min per g). Mismatch between blood flow and 18-FDG uptake, with a single exception, was not observed in any segment with blood flow <0.25 ml/min per g. All dyskinetic segments (n=5) also had blood flow <0.25 ml/min per g. In 23 patients with 45 myocardial segments with normal contraction or only mild hypokinesia, 43 of the 45 segments had flow >0.39 ml/min per g (average flow 0.78 +0.35 ml/min per g).

In patients with chronic myocardial infarction, myocardial viability is unlikely when basal regional myocardial blood flow was <0.25 ml/min/g. Average basal flow in segments with normal or nearly normal wall motion was 0.78 +0.35 ml/min/g. PET measurement of regional myocardial blood flow was helpful in identifying nonviable myocardium in these patients.

Safety issues: The radiation dose associated with the N-13 ammonia study was 5 mR/mCi for whole body and 51 mR/mCi to the bladder (target organ). The radiation dose associated with the F-18 deoxyglucose study was 39 mR/mCi for whole body and 440 mR/mCi to the bladder (target organ). No other safety issues were addressed.

Commentary: Although the primary hypothesis of the study does not relate to a direct assessment of myocardial perfusion in the evaluation of CAD using N-13 ammonia PET as compared to another perfusion standard, myocardial perfusion assessment can still be commented upon. Indirect measurements such as regional wall motion on ventriculograms (21 of 26 patients), radionuclide ventriculograms (3 of 26 patients), and echocardiograms (2 of 26 patients) were obtained to permit comparison of PET perfusion results.

Because myocardial blood flow is needed to maintain aerobic metabolism in normal contractile myocardial cells, lack of flow leads to oxygen deprivation in myocardial cells and impaired contractility. Abnormal wall motion is one of many consequences of ischemia. This study uses wall motion as a marker for ischemic conditions and consequently compares PET perfusion results to severity of wall motion abnormality. Study results support the correlation that the more severe the wall motion abnormality, the lower the perfusion rate. All dyskinetic segments (n=5) had perfusion <0.25 ml/min per g; 43 out of the 45 myocardial segments with normal contraction or only mild hypokinesia had flow >0.39 ml/min per g.

Several strengths of the study are evident. The PET blood flow results were objectively computed using a mathematical model and were made without knowledge of regional wall motion results. The ventriculograms, for wall motion, were assessed without knowledge of the PET results. Thus, the description of PET blood flow values by wall motion abnormalities provided objective information that could be used in the final assessment of myocardial viability. The patient population of those with documented myocardial infarction is an appropriate one to identify nonviable myocardium quantitatively by PET measurements. Lastly, coronary angiography was used to assess stenosis severity and the PET blood flow data were correlated to these results. These results described the blood flow for non-stenosed, >50%, and <50% stenosed vessels.

One concern the study raises is that PET scans and angiograms were done at differing points in the patients' clinical course. The time from myocardial infarction to PET scan (2-192 months, mean 44 months) and the time from PET scan to cardiac catheterization (mean of 5 + 4 months (SD), with 72% of patients having catheterization performed within 3 months of PET study) is quite variable. Study endpoints such as wall motion, perfusion, and myocardial metabolism may be time-sensitive from infarct and results may need to be stratified by time rather than analyzed as a group. It may also be important to minimize time between each test to facilitate comparisons.

The study did not mention how stenoses were determined or how these were calculated from the coronary angiograms. Another concern is ventriculograms were interpreted by only one reader. This reader was, however, masked to the PET results. While this eliminates inter-reader variability, there is subjectivity in reading ventriculograms. However, as ventriculography is a

common and familiar procedure, the expectation is that the reader would be accurate. Of note, while most ventriculograms were obtained during catheterization, 5 patients had either radionuclide ventriculograms or echocardiogram wall motion assessment.

This study concluded that the rate of myocardial blood flow measured by N-13 ammonia PET was correlated with degree of wall motion abnormality. The results of PET in this study demonstrated biological consistency with current understanding of consequences of low perfusion states on myocardial wall motion. It supports the functional uses of N-13 ammonia PET perfusion results.

3. Other published studies

Although their study hypotheses differed widely, the studies below provided supporting information of N-13 ammonia efficacy for assessing myocardial perfusion in the evaluation of CAD.

a. Laubenbacher C, Rothley J, Sitomer J, Beanlands R, Sawada S, Sutor R, Muller D, Schwaiger M. An automated analysis program for the evaluation of cardiac PET studies: Initial results in the detection and localization of coronary artery disease using nitrogen-13-ammonia. J Nucl Med 1993; 34:968-978.

This study was conducted at the University of Michigan Medical Center. An automated quantitative analysis method applied to myocardial N-13 ammonia PET rest/pharmacological stress data was evaluated to determine N-13 ammonia PET's diagnostic performance. The study also developed diagnostic criteria for stress-induced perfusion abnormalities for each vascular territory. A control group of 23 subjects without evidence of coronary artery disease (and who did not undergo angiography) and 29 patients with angiographically confirmed coronary artery disease were studied.

The study concluded that high diagnostic accuracy for detection and localization of coronary artery stenosis in predefined vascular territories were possible using this new methodology of volumetric data sampling and mathematical constraints of activity sampling to the expected shape of the left ventricle. Detailed sensitivity and specificity data stratified by each of the major coronary arteries under stress and rest conditions for detecting CAD using a range of angiographic stenosis percentages are presented. Using a threshold of >75% stenosis diameter within a given vascular territory, the authors report sensitivity was 93% and the specificity was 80%. Receiver operator curves for overall detection and localization of CAD in individual vascular territories are given. Interobserver and intraobserver variability for each vessel territory is plotted as a linear regression. Detailed charts of inter and intraobserver agreement on detection and localization of CAD shows good agreement (between 80-97%).

Strong points of the study include use of angiography as the standard of truth, use of computerized PET perfusion quantification, and the use of an agreement study between two masked readers versus the computerized PET quantification program. Readers re-read images with a high degree of reproducibility. Reader agreement was calculated for different anatomical regions. The high level of details in the published report about methodology, data (including vessel territory data), and inter and intraobserver performance support the high quality of this study. The correlation of PET results and angiographic stenosis of >90% in rest to stress evaluations range from 77% to 100% depending upon vessel.

b. Di Carli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, Czernin J, Rokhsar S, Stevenson LW, Laks H, Hawkins R, Schelbert HR, Phelps ME, Maddahi J. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994; 73:527-33.

This study was conducted at the University of California Los Angeles School of Medicine. This study was done with 93 consecutive patients with angiography-defined coronary artery disease and severe left ventricular dysfunction (mean left ventricular function of 0.25). It assessed the prognostic value of PET mismatch of the ammonia and glucose uptake scores and the interrelation between PET mismatch pattern and choice of medical therapy or revascularization for predicting survival and improvement in symptoms of heart failure. Follow up was for an average of 13.6 months (range 2 to 31 months).

Patients with severe left ventricular dysfunction and CAD may have less mortality with

revascularization. However, surgical mortality is high for these patients. The ability to predict beneficial effects of revascularization would be to improve blood flow to hypoperfused regions that have living myocardium (but may be contracting less optimally due to ischemia) to improve left ventricular function. N-13 ammonia perfusion assessment coupled with 18-FDG metabolism was hypothesized to have a role in this prediction.

All patients were potential candidates for myocardial revascularization and had a resting, myocardial perfusion (N-13 ammonia) and glucose uptake (18-FDG) PET study. Diabetics, hypertensives, patients with pulmonary disease, heart failure, or angina, were included. Patients were followed up for death and its cause. Fifty patients eventually underwent medical therapy and the rest (43) revascularization.

The results suggest that the presence of mismatch (segmental glucose uptake by 18-FDG was increased relative to perfusion) in patients with CAD and severe LV dysfunction is associated with poor annual survival with medical therapy [i.e., are at higher risk of cardiac death during follow-up] compared to those who had revascularization. Revascularization in patients with PET mismatch appeared to be associated with improved survival and decreased symptoms of heart failure.

This study supports the use of N-13 ammonia in assessment of myocardial perfusion in the evaluation of CAD by contributing clinical endpoints of survival and mortality to the interpretation of PET. The results obtained are consistent with the biologic plausibility that PET metabolism and perfusion mismatch assesses physiologic aspects of microperfusion not appreciated by angiography alone. This study is consistent with the PET studies of Gewirtz on wall motion. It goes further by having outcomes data that support N-13 ammonia PET's assessment of perfusion. The results support the clinical significance of PET myocardial perfusion measurements.

c. Gould LK, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. 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 for healing coronary endothelium. Circulation 1994;89:1530-38.

This study from the University of Texas Medical School is a randomized study. Fifteen patients with CAD documented by a 50% or more diameter stenosis in one or more major epicardial coronary arteries on coronary angiography were assessed for short-term (90 day) effects of cholesterol lowering programs on perfusion as measured by rest-dipyridamole N-13 ammonia PET. Patients served as their own control in pre- and post- intervention studies. Completely automated, objective measures of size and severity of perfusion abnormalities on rest-dipyridamole PET images were made by computer algorithm. Results of PET image evaluations, serum lipid profiles, and clinical evaluation using the Bruce protocol showed improvement during treatment and reversal of improvement on treatment withdrawal. The authors suggest that myocardial perfusion and CAD can be followed non-invasively by dipyridamole PET.

This study's strength lies in the use of multiple complementary endpoints, including clinical performance on the Bruce protocol, to support PET findings of altered perfusion. Use of an automated system to measure PET perfusion addresses concerns of observer bias and variability. While the study is small, the consistent results across treatment groups and across endpoints supports the usefulness of PET in myocardial perfusion imaging to assess CAD. This study also supports the clinical significance of PET myocardial perfusion data.

d. Beanlands RSB, Muzik O, Melon P, Sutor R, Sawada S, Muller D, Bondie D, Hutchins GD, Schwaiger M. Noninvasive quantification of regional myocardial flow reserve in patients with coronary atherosclerosis using nitrogen-13 ammonia positron emission tomography: Determination of extent of altered vascular reactivity. J Am Coll Cardio 1995; 26:1465-75.

This study was conducted at the University of Michigan Medical Center. The study evaluated patients with coronary artery disease to determine the relation between regional myocardial blood flow reserve measured by N-13 ammonia kinetic modeling and stenosis severity assessed by quantitative angiography, and examine whether flow reserve is impaired in regions supplied by vessels without significant angiographic disease.

Twenty-seven subjects were enrolled and classified into three groups: 1) 5 young healthy

volunteers, 2) 7 middle aged volunteers with low likelihood for CAD, and 3) 15 patients with angiographically confirmed coronary artery disease (>50% stenosis by quantitative coronary angiography with 9 of the 15 having at least one vessel disease >90% stenotic). All subjects underwent N-13 ammonia PET rest/pharmacological stress studies and group 3 patients underwent coronary angiography (PET and coronary angiography were performed within a mean of 3.5 +7 days of each other). All of group 3 patients' data on vessel anatomy, percent area stenosis, minimal lumen diameter, flow rates at rest and with stress, myocardial flow reserve, collateral flow and stenosis severity category were presented in detail.

Results indicated flow reserve as measured by PET had a correlation coefficient of r=-0.56 with percent stenosis on angiogram (fair inverse correlation-the higher the flow reserve the smaller the percent stenosis) and a correlation coefficient of r=0.75 with minimal lumen diameter on angiogram (good correlation).

The study concluded that there was a progressive reduction in myocardial flow reserve, as measured by N-13 ammonia PET, with increasing angiographic disease severity. Among patients with coronary disease, myocardial regions without significant angiographic stenoses displayed reduced flow reserve in regions as compared to control subjects.

The study used quantitative angiography data compared to quantitative PET results. A variety of subjects with different clinical conditions were tested, however, only 9 of 27 subjects had severe CAD of >90% stenosis. The study also used a variety of angiographic stenosis parameters, studied multiple vessels per patient using angiography and PET, determined PET flow rates and myocardial flow reserve for each vessel, and compared PET to angiography using these diverse factors. These parameters supported correlation between angiographic results and PET results. This study's consistent finding of good correlation, r=0.75, between angiography stenosis and PET flow rates, its detailed presentation of vessel and patient data, and the use of objective measurements provide support for the use of N-13 ammonia PET in assessing myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions.

e. Czernin J, Barnard RJ, Sun KT, Krivokapich J, Nitzsche E, Dorsey D, Phelps ME, Schlebert HR. Effects of short-term cardiovascular conditioning and low-fat diet on myocardial blood flow and flow reserve. Circulation 1995;92:197-204.

This study from the University of California School of Medicine at Los Angeles measured response of myocardial blood flow and flow reserve to cardiovascular conditioning together with a low-fat diet. The study hypothesis was that cardiovascular conditioning with a low-fat diet would lead to changes in hemodynamics, serum lipids, and exercise performance, along with increased blood flow as measured by N-13 ammonia PET. The study group consisted of 13 volunteers, of whom 4 had CAD, none of whom were on any lipid lowering, cardiac, or antihypertensive medications. The nonrandomized and non-concurrent control group consisted of 8 normal volunteers. Quantification of myocardial blood flow at rest and during dipyridamole-induced stress was done using a semi-quantitative image analysis program. With intervention, resting rate-pressure product, serum cholesterol, and resting flow rate decreased while hyperemic blood flow increased resulting in improved myocardial flow reserve. No changes were observed with controls. Correlation coefficients were calculated between PET measurements and clinical parameters listed above and results were moderate to good.

The results of this study provide support for clinical endpoints (such as rate-pressure product and improved exercise capacity) correlating with PET myocardial flow reserve measurements. While it may seem intuitive that increased myocardial perfusion should lead to improved rate-pressure product and improved exercise capacity, these results confirm the biologic plausibility of PET results. While small in size, the endpoints are clinically relevant to coronary perfusion, they are assessed objectively, and there is a high level of detailed data on patients. This study supports N-13 ammonia PET in evaluating myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions.

f. Gould LK, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, Mullani N, Bolomey L, Dobbs F, Armstrong WT, Merritt T, Ports T, Sparler S, Billings J. Changes in myocardial perfusion abnormalities by PET after long, intense risk factor modification. JAMA 1995;274:894-901.

This randomized, controlled trial quantified changes in size and severity of myocardial perfusion abnormalities by rest-dipyridamole PET in patients with documented CAD on initial coronary angiography who either underwent risk factor modification (n=20) or usual care (n=15). Both quantitative coronary angiography and quantitative PET imaging were done at baseline and 5 years after randomization. Results showed the risk factor modification group had improved size and severity of perfusion abnormalities on dipyridamole PET compared to controls. The relative magnitude of changes in size and severity of PET perfusion abnormalities was comparable to or greater than the magnitude of changes in percent diameter stenosis, absolute lumen area, or stenosis flow reserve documented by quantitative coronary angiography.

The study's design is well-conceived. The report contained agreement data on visual interpretation versus the automated PET program results. It also contained the drop out rates for each group (5 of 20 controls dropped out and 8 of 28 patients in the intervention group dropped out). Because the trial is itself very small, there is concern about bias introduced with these drop outs. However, there are high quality, quantitative comparison data involving PET imaging compared to coronary angiography data in pre- and post-intervention which support use of N-13 ammonia myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions.

g. Sambuceti G, Parodi O, Giorgetti A, Salvadori P, Marzilli M, Dabizzi P, Marzullo P, Neglia D, L'Abbate A. Microvascular dysfunction in collateral-dependent myocardium. J Am Coll Cardiol 1995; 26:615-23.

This study was conducted at a clinical site in Pisa, Italy. The study evaluated myocardial blood flow regulation in collateral-dependent myocardium of patients with angina and coronary artery disease. Nineteen patients with angina and angiographically confirmed coronary artery disease as well as a comparison group of 13 normal subjects were enrolled. Rest/pharmacologic and/or external pacemaker (pacing-induced tachycardia) stress (dipyridamole) N-13 ammonia PET imaging studies were performed on all subjects.

Patients with stable angina and single-vessel disease may have a dysfunction of the resistive vessels that decrease the vasodilatory capacity in areas supplied by angiographically normal coronary arteries. This microvascular dysfunction might affect blood flow regulation. The authors hypothesized that use of N-13 ammonia to assess perfusion in collateral-dependent areas at rest and stress may provide more functional information of the microvasculature in these regions.

The angiographic score of collateral circulation was not associated with differences in baseline myocardial perfusion or function. During pacing, myocardial blood flow was similar in the six patients with well visualized and in the five patients with poorly visualized collateral circulation. However, the angiographic score of collateral circulation was associated with differences in the degree of flow inhomogeneity. The ratio between flow in collateral-dependent regions and in remote regions used as "control" areas was lower in patients with poorly developed collateral vessels during pacing and after dipyridamole compared to those with good collaterals.

The study concluded that despite a reduced blood flow at rest, collateral-dependent myocardium maintains a residual blood flow reserve that is almost fully used during increased oxygen consumption.

This study allowed comparison of angiographic data and quantitative PET imaging data in a variety of subjects, including those with severe CAD. (Di Carli (1994) and Haas (1997) identified lack of correlation between angiography and PET in patients with severe CAD.) Normal subjects who had atypical chest pain who were referred to coronary angiography were also included. All angiograms were done at or less than two weeks before the PET study. This makes it unlikely that the patient's CAD may have worsened or improved, impacting on the comparability of the patient's PET and angiogram. The study is consistent with Di Carli and Haas. Angiography and PET contribute different information about perfusion making complete correlation between these tests throughout the vast clinical spectrum of the disease unlikely.

h. Soufer R, Dey HM, Lawson AJ, Wackers FJT, Zaret BL. Relationship between reverse redistribution on planar thallium scintigraphy and regional myocardial viability: A correlative PET study. J Nucl Med 1995; 36:180-187.

This study was conducted at the Department of Veterans Affairs Medical Center, West Haven, Connecticut. A study group of 32 patients with documented chronic coronary artery disease and demonstrated reverse redistribution, defined as a new or increased defect on planar thallium-201 scintigraphy after stress, were enrolled. The mean age was 66 years. All patients were maintained on existing medication. All patients underwent both planar thallium-201 rest/stress scintigraphy and N-13 ammonia and F-18 deoxyglucose (18-FDG) PET viability imaging. Radionuclide angiography was performed to obtain wall motion on 23 of 32 patients. After study, all patients were followed up for 9 to 19 months.

The purpose of this study was to assess myocardial viability via PET in the area of reverse distribution on planar thallium-201 scintigraphic images and determine the prognostic value of reverse distribution and PET imaging after a mean follow-up period of 14 months. The mechanism that explains reverse redistribtution is uptake of thallium-201 by the interstitial compartment of a necrotic area and faster washout rate of thallium-201 from this compartment than adjacent normal myocardium. The defect on imaging is only seen on redistribution imaging. This phenomenon has been associated with higher mortality for patients with previous myocardial infarction. Additional information on pathophysiology was obtained through application of PET to the phenomenon of reverse redistribution in this study.

Fifty segments showed reverse redistribution on thallium-201 images. Nineteen segments were normal on PET 18-FDG and N-13 ammonia scan. Seventeen had mismatch defined as a region with severely reduced blood flow with a relative increase of FDG that was greater than 50% of activity in the reference region and within two standard deviations of reference mean values for that segment as defined by a normal database. A total of 36 of 50 segments (72%) of reverse redistribution were PET defined as viable. Sixty-one percent (11 of 18) of segments with abnormal regional wall motion and reverse distribution were PET scar. After mean follow up of 14 months, 5 of 10 patients that had cardiac events had severe reverse redistribution and PET mismatch (viability) compared to 2 of 22 patients without cardiac events.

Using measurements of PET regional blood flow, the study concluded that the majority of thallium reverse redistribution segments was PET viable as judged by

18-FDG uptake. PET viability in areas of reversed distribution is not inferred by regional wall motion analysis. Regional PET mismatch, indicating viable myocardium with perfusion abnormality, and severe redistribution were both associated with an increased frequency of cardiac events.

This study used careful anatomical correlation of planar thallium imaging and N-13 ammonia/FDG data. It demonstrates different pathophysiologic information is obtained from these two modalities concerning reverse redistribution found in CAD patients undergoing thallium-201. Clinical significance of this information is obtained through patient follow up to track cardiac events. The study supports the physiologic assessment of perfusion by N-13 ammonia PET.

i. Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, Schwaiger M. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. J Am Coll Cardiol 1997; 30:1693-700.

This retrospective study was conducted at a clinical site in Munich, Germany. The study was masked and investigated whether determination of tissue viability by means of PET imaging before coronary artery bypass graft surgery affects clinical outcome with respect to both in-hospital mortality and 1-year survival rate.

The basis for this hypothesis is stated above in the review of Di Carli, Davidson, Little, et al., 1994.

A group of 76 patients with advanced three vessel and angiographically confirmed CAD and severe LV dysfunction who were considered candidates for coronary artery bypass graft (CABG) surgery were retrospectively selected and had N-13 ammonia and 18-FDG PET imaging studies performed.

The study concluded selection of patients with

impaired left ventricular function based on extent of PET- defined viability (perfusion/metabolism mismatch) supplementary to clinical and angiographic data may lead to

postoperative recovery with a low early mortality and promising short-term survival.

This study is consistent with that of Di Carli, which showed collateral circulation is not fully detected by angiography. PET results provide somewhat different perfusion information in patients with severe CAD from those obtained by angiography. This consistency of results in patients with severe CAD across institutions and across continents supports the use of N-13 ammonia for perfusion assessment. It is also consistent in demonstrating that myocardial perfusion in the evaluation of CAD can not be completely understood through angiography results alone. In this study, PET perfusion data was associated with a clinical outcome, mortality. This study supports the clinical significance of PET perfusion data.

4. The following articles were reviewed for support of N-13 ammonia PET myocardial perfusion quantification by computer programming.

Krivokapich J, Smith GT, Huang SC, Hoffman EJ, Ratib O, Phelps ME, Schelbert HR. N-13 ammonia myocardial imaging at rest and with exercise in normal volunteers: Quantification of absolute myocardial perfusion with dynamic positron emission tomography. Circulation 1989; 80:1328-37.

Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990; 15:1032-42.

Gerwirtz H, Skopicki HA, Abraham SA, Castano H, Dinsmore RE, Alpert NM, Fischman AJ. Quantitative PET measurement of regional myocardial blood flow: Observations in humans with ischemic heart disease. Cardiology 1997: 88:62-70.

These are three of several papers that have described and validated radiopharmaceutical kinetic compartmental models to determine regional myocardial blood flow with rest/stress PET imaging using N-13 ammonia in normal volunteers. In addition to studying normal volunteers, the third paper studies patients with angiographically confirmed ischemic heart disease and proposes a new methodology that uses a single measurement of adenosine stimulated myocardial blood flow to assess coronary artery stenosis severity.

These papers form the basis and extension of the methodology for quantitatively determining regional myocardial blood flow with PET N-13 ammonia as used in subsequent studies of cardiovascular disease.

C. Discussion of Efficacy Data for Coronary Perfusion

The effectiveness data supporting the indication for N-13 ammonia PET imaging for myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, is derived from the published medical literature. As outlined in FDA's guidance for industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), FDA can, in certain circumstances, rely on published reports alone to support approval of a new product. FDA has outlined factors that increase the possibility of reliance on published reports alone to support approval of a new product. These include: 1) multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where findings across studies are consistent; 2) a high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), study endpoints, and a full accounting of all enrolled patients; 3) clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment; 4) robust results that yield a consistent conclusion of efficacy and do not require selected post hoc analyses; 5) conduct of studies by groups with properly documented operating procedures. As a body of literature taken together, the reviewed studies provide the cumulative evidence to support effectiveness of N-13 ammonia PET to assess myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, for patients suspected of having the disease or who have an existing diagnosis of CAD.

Five masked, controlled, comparison studies of N-13 ammonia PET imaging for myocardial perfusion in the evaluation of CAD and recognized standard for perfusion, angiography, or with appropriate clinical functional standards, such as wall motion, are discussed above in II(B)(1) and II(B)(2). Nine supporting studies in II(B)(3) are also cited where myocardial perfusion in the evaluation of CAD is compared to a variety of standards including exercise tolerance as well

as coronary angiography, however, the main hypotheses of these studies varied considerably. Nevertheless, these studies provide direct or indirect information on the functional assessment abilities of N-13 ammonia PET and have some clinical outcomes data. All the studies, conducted by different investigators in different populations with different disease spectrum, performed over a number of years, allowed evaluation of N-13 ammonia myocardial blood flow through comparison with an identified perfusion standard or clinical outcome.

New diagnostic tests are ideally evaluated in clinical trials with the target population, meaning people with the suspicious condition, including those who are suspicious for having the disease but don't have it. Initial phase 1 and phase 2 studies on a new technology typically are carried out with pre-defined populations of diseased and non-diseased patients. Confirmatory clinical assessment of the test in the larger target population provides more meaningful information on the test's performance ability. This is because sensitivity and specificity will vary depending on the characteristics of the population in which the test is used. In the literature search and review of articles, no studies were found performed with a healthy, asymptomatic population to detect CAD as part of a screening setting. Therefore, use of N-13 ammonia PET to assess myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, is only supported in the diagnostic setting, where patients are suspected of having the disease or have an existing diagnosis of CAD.

The majority of studies did not include a prospective population for which the test is intended. However, the two studies that did enroll patients prospectively and utilized a direct comparison of anatomy as measured by angiography to perfusion measured by PET were in II(B)(1): Gould (1986) and Demer (1989) (the latter being the continuation of the initial report of the former). Both Gould and Demer found consistent and strong correlation with PET perfusion measurements and angiographically defined CAD. Because perfusion and CAD were continuous in nature, the authors did not calculate sensitivity and specificity by forcing findings into dichotomous outcome variables. However, 2 x 2 tables were constructed by FDA using the detailed data presented in Demer's study, along with an assumption. The sensitivity and specificity of N-13 ammonia using the stated approach was acceptable.

Schelbert (1982) retrospectively selected 32 patients with CAD who had angiography results, along with 13 normal volunteers. Di Carli (1994) enrolled 42 consecutive patients with CAD proven by a previous catheterization study to assess myocardial viability correlation with wall motion, 18-FDG metabolism, and stenosis. Gewirtz (1994) assembled a prospective cohort of 26 patients to study correlation of flow rates and myocardial viability, but enrollment was limited to patients who had a previous catheterization study and documented CAD on catheterization. These latter three studies either presented data (Schelbert (1982)), or may contain raw unpublished data (Di Carli (1994) and Gewirtz (1994)) on sensitivity of PET with respect to angiography in detecting CAD. Schelbert (1982) also included a subgroup of 11 patients who underwent thallium-201 exercise testing and presented detailed study results: numbers and locations of diseased vessels were identified and comparisons of PET results (for the entire study and specific vessels) to angiography, "truth."

The Gould (1986) and Demer (1989) studies can be viewed as comparative studies between N-13 ammonia and angiography allowing for calculation of sensitivity and specificity. In other studies, angiography defined "truth" with respect to CAD for sensitivity, but specificity was calculated based on an "assumed truth" that normal volunteers did not have CAD. The reviewed studies of Schelbert (1982), Laubenbacher (1993), Beansland (1995) and Gould (1995), supported reproducible and robust correlation between angiography and N-13 ammonia PET, particularly in patients with mild and moderate CAD. These results suggest that N-13 ammonia PET perfusion results are comparable to angiography for anatomical assessment in particular patients.

Other comparative trials assessed the correlation of N-13 ammonia PET to a variety of standards to investigate functional microperfusion. The latter studies did use angiography to identify collaterals, but as mentioned in the beginning of this review, angiography may not be the appropriate standard for functional perfusion.

Studies that focused on functional hypotheses, such as Gewirtz (1994), Haas (1997), Czernin (1995), Di Carli (both 1994 studies), Sambucetti (1995), Gould (1994), and Soufer (1995), demonstrated that correlation with angiography results was not good in patients with severe CAD and left ventricular dysfunction. However, these authors and others used standards to assess cardiac function, such as exercise tests, and clinical outcomes to provide additional

information with which N-13 ammonia results were consistent. These other standards of assessment provided clinical correlation regarding the N-13 ammonia PET perfusion results. These multiple studies conducted by different investigators in different institutions, in different time periods contained detailed information on study plans and results that support PET's use in functional perfusion assessment.

The reviewed studies did not state a priori criteria for the amount of correlation between N-13 ammonia PET and the comparative standard considered satisfactory, sample size calculation based on an a priori power, nor type I and type II error limits. However, enough raw data was presented to allow adequate determination of N-13 ammonia testing performance. When appropriate, the FDA statistician calculated confidence intervals for sensitivity and specificity to better understand the precision around the point estimates.

The types of enrolled subjects varied widely in the studies. Normal volunteers were studied with N-13 ammonia PET along with retrospectively selected, angiographically-defined patients, and consecutively enrolled CAD patients. Definitions of significant stenosis varied as did definitions of CAD. CAD patient selection varied from study to study on percent stenosis on angiogram, presence of left ventricular dysfunction of a certain amount, and exercise tolerance results. For example, prospective subjects from the Gould (1986) and Demer (1989) papers were enrolled with indications for angiography, such as chest pain or abnormal ECG findings, as part of the study entry criteria. These included subjects who ultimately had normal angiographic results as well as subjects who had coronary artery stenoses. Taken together, the studies did contain patients that appeared to reflect the diverse spectrum of disease and disease-free states to support the broad application of N-13 ammonia in the population in which further diagnostic testing concerning myocardial perfusion in the evaluation of CAD might be used. These studies also demonstrated that in certain patient disease circumstances, N-13 ammonia functional perfusion testing provides additional information from angiography.

While many of the initial studies originated from a few institutions, the recent N-13 ammonia PET studies are from many different institutions and countries with independently supportive results. Although the total numbers of patients in most studies were small, taken as a whole the numbers are meaningful. There are additional studies published in the medical literature, not included in this review because they did not allow a comparative evaluation. Many of these studies support the use of N-13 ammonia in myocardial perfusion in the evaluation of CAD by providing consistent information on functional assessment. For example, nitroglycerin use and N-13 ammonia PET showed topical nitroglycerin alters myocardial perfusion by preferentially increasing flow to areas of reduced perfusion with little or no change in global perfusion in patients with angina responsive to nitroglycerin (Fallen, E. et al. Redistribution of myocardial blood flow with topical nitroglycerin in patients with coronary artery disease. Circulation. 1995;91:1381-1388.) This study had no imaging or functional standard comparator but the results support the biologic plausibility of N-13 ammonia PET to assess functional perfusion.

The selection of measurement outcomes with N-13 ammonia has varied from study to study. Early studies had to handle problems of ascertainment bias because of subjective scoring or evaluation of images both from N-13 ammonia PET and angiography or other imaging. There were problems with translating the "gold standard's" two-dimensional picture to accurately correlate with flow and there were usually issues of patient positioning. N-13 ammonia also has known issues: potential dependence of extraction and retention of N-13 ammonia in myocardium on the metabolic status of the heart and a reduced retention on N-13 ammonia on the posterolateral wall of the normal heart. Evolution in the imaging and medical physics field has allowed for digitized images with computer modeling to address many concerns and to generate calculations of flow reserve for both angiographic data and PET scans. This allows for objective quantification of MBF, which enhances reproducibility.

Reader performance is also important in studies. The amount of experience readers had with N-13 ammonia imaging in the cited studies is not mentioned. It is an assumption that performance as reported in the studies can be replicated in the practicing community. Oftentimes, however, studies report the better spectrum of reader performance reflecting publication bias. Nevertheless, the results are consistent across the different studies, different institutions, and different time periods supporting independence of the findings.

Inter-reader variability is also important to assess if a study utilizes more than one reader. Studies using one reader do not have inter-reader variation; however, these studies do not capture the scope of variation possible in reader assessment of scans when N-13 ammonia PET

is used more widely. The reviewed studies cited often made attempts to quantify and address inter-reader variability in N-13 ammonia PET readings. Many utilized more than one reader. Multiple readers decrease variability, because as the number of readers increases, variability of the median rating or score usually decreases. Many studies, however, did not provide information on how angiograms were read. These might also be subject to inter-reader variability, but readers would most likely have more familiarity and experience with angiographic images. Criteria for dispute resolution, which is needed whenever a study uses more than one reader, were also only occasionally mentioned. As technology improved to allow for computerized measurement and reproducibility, issues of inter-reader variability and dispute resolution became less important. These latter studies, utilizing objective quantification of myocardial perfusion, demonstrated the results found in earlier studies were robust. These latter studies suggest that inter-reader variability issues in the earlier studies, which used subjective interpretation by readers, are not a major influence.

Some studies cited also made attempts to minimize bias by using randomization and masking. Randomization in these studies was done in the time period when computerized readings were not available. N-13 ammonia PET images were presented to interpreting physicians in a random manner. The readers were also masked to the clinical data of patients, or their angiography (or other comparative technology) results. In more recent times, computerized quantification of PET and angiographic results has made randomization and masking less important. Nevertheless, the study protocol should ensure that biases from technicians, as well as investigators, who acquire, process, and record computerized results are controlled. These studies are from the literature and it is not possible to conduct scientific audits at this time. Again, because the latter studies using computerized measurements obtained consistent results as earlier studies using subjective criteria, bias appears to be a minimal concern in the studies.

Given the consistency of findings for anatomical and function perfusion assessment throughout the almost twenty years of published studies reviewed, the reproducibility of results in many different institutions with different investigators, the reproducible correlation with angiography (an accepted external truth standard) in patients with mild to moderate CAD, the correlation with current functional standards of perfusion in patients with severe CAD and left ventricular dysfunction, this review supports the effectiveness of N-13 ammonia for assessing of myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, for patients suspected of having the disease.

III. **Safety Evaluation**

N-13 ammonia PET radiopharmaceutical is radioactively labeled ammonia. It is administered intravenously for PET imaging. The overall adverse reaction profile of N-13 ammonia is well understood after roughly a quarter century of clinical use. N-13 ammonia PET is performed in North America, Japan, Europe, Australia, and other countries.

Because ammonia is a ubiquitous substance in the body, its metabolism and excretion is well understood. N-13 ammonia is rapidly metabolized to N-13 urea, N-13 neutral amino acids, and small amounts of N-13 acidic amino acids. N-13 urea, the main circulating metabolite of N-13 ammonia, is eliminated through the urine.

The FDA biopharmaceutical reviewer of N-13 ammonia published studies reports that the dose range was from 8 to 25 mCi. The specific activity range was reported as 200-400 mCi per micromole from Rosenspire (1990). The biopharmaceutical reviewer estimates that the amount of N-13 ammonia administered for the 8 mCi dose is 0.02-0.040 micromoles and 0.0625-0.125 micromoles of N-13 ammonia for the 25 mCi dose. Thus, the amount of ammonia administered is very small compared to the amount of ammonia already produced in the body. The blood ammonia concentration in a normal person is less than 35 micromoles per liter. Thus the amount introduced by N-13 ammonia PET imaging is not significant compared to the circulating level of ammonia in the body.

Radiation exposure from N-13 ammonia is a known risk. The amount of N-13 ammonia injected in the above reviewed studies was usually one intravenous dose of 10-20 mCi N-13 ammonia for the rest portion and another similar dose for the stress portion of the PET scan. For doses up to 25 mCi, data provided by the International Commission on Radiation Protection allows estimation that the urinary bladder absorbs 0.75 rem, an acceptable level. Higher radiation values are stated in two studies found in this literature review (Gewirtz (1994) and Meyer (1995)) suggesting there are differences in dosimetry data determined by different

investigators in different laboratories.

The physical half-life of N-13 is about 10 minutes for decay from N-13 ammmonia to carbon-13. The effective blood elimination half-life based on data from Rosenspire (1990) is 2.2 minutes. The short physical half-life of N-13 permits sequential evaluations and avoids high radiation exposure for patients. However, the short half-life requires an on-site cyclotron for manufacture and sophisticated radiochemical synthesis and purification procedures.

The N-13 ammonia PET studies which had a rest and a stress component, involved monitoring of cardiovascular parameters, such as heart rate, blood pressure, and the rate pressure product. These measurements are reported in many papers for normal and CAD patients. These reports show an increase in the blood pressure and heart rate associated with the hyperemic/stress component of the test, as is expected. There were no comments on any increase in blood pressure or heart rate with injection of N-13 ammonia. There is no specific reference to any patient having an acute effect with N-13 injections.

In the published literature concerning safety of PET drugs, in 1996, Edward Silberstein, Janet Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine published in the Journal of Nuclear Medicine in a five year prospective study of 18 collaborating institutions. The study used a questionnaire that enumerated monthly the number of procedures used and the adverse reactions noted for radiopharmaceuticals and non-radioactive drugs used in nuclear medicine. The study utilized operational definitions for adverse reactions and significant adverse reactions and devised an algorithm to categorize probability of causation. The published study included a copy of the actual questionnaire, which required itemization of any and all radiopharmaceuticals administered, adverse reactions to radiopharmaceuticals, dose, route, reaction, etc., as well as total non-radiopharmaceuticals (such as adenosine or dipyridamole) administered and adverse reactions to these agents. No reactions are reported for N-13 ammonia. The study also performed a reference check of listed adverse reactions by references and no adverse reactions were listed by the U.S. Pharmacopeial Convention's Drug Information for the Health Care Professional, 1995. Dr. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine also conducted a retrospective and prospective study of the prevalence of adverse reactions to PET radiopharmaceuticals published in 1998 in the Journal of Nuclear Medicine. In this updated study, Dr. Silberstein reported 22 PET centers provided monthly adverse reaction data from 1994 to 1997 related to PET drug administration in 47,876 dosages. In addition, retrospective data was collected from the opening of these centers on 33,925 radiopharmaceutical dosages. In no case were there any adverse reactions.

The published clinical trials literature is not an appropriate data base to evaluate chemistry and manufacturing safety issues related to drug purity and identity. Different production pathways may lead to different concentrations of N-13 ammonia and to different by-products and impurities. These specific topics will be addressed by the FDA PET Chemistry and PET Good Manufacturing Practice working groups.

Because radiation is a known carcinogenic and mutagenic agent, standard radiation precautions for using PET with respect to patients, pregnant women, and occupational exposure are needed.

IV. **Conclusions**

The well-controlled studies of Gould (1986) and Demer (1989) permit an estimate of N-13 ammonia's performance for assessing myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, for patients undergoing cardiac catheterization for the diagnosis of CAD. These two studies together provide correlation with angiography data. This is independently corroborated in studies by Schelbert (1982), Laubenbacher (1993) and Beansland (1995). In other comparative studies of N-13 ammonia PET with angiography, thallium-201, exercise stress testing, and clinical outcomes of survival and cardiac-specific mortality, N-13 ammonia PET's ability to detect myocardial perfusion in microvasculature is supported by myocardial regions with scarring, wall motion abnormality, non-angiographically defined collaterals or angiographically present collaterals, thallium-201 reverse redistribution, and effects of lifestyle interventions such as low fat diet with exercise on coronary circulation. N-13 ammonia is a minimally invasive test, requiring intravenous injections, and may be used to complement or provide an alternative to existing coronary perfusion tests for certain patients.

The above referenced published medical literature and the cumulative experience support the

claim for the use of N-13 ammonia used in positron emission tomography to assess myocardial perfusion in the evaluation of CAD, following separate administration under rest and stress conditions, for patients suspected of having the disease or who have an existing diagnosis of CAD. Safety of N-13 ammonia in the medical literature is supported by the absence of documented adverse events, the knowledge of ammonia metabolism and its safety profile, and the known radiation risk associated with its production, handling, and use. Specific chemistry and manufacturing issues are deferred to the FDA working groups on these issues.

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Florence Houn, MD MPH date

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Sonia Castillo, PhD date

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Appendix A: Figure 3 Plots of SFR and PET Defect Severity Scores from Demer LL, Gould LK, Goldstein RA, Kirkeeide RL, Mullani NA, Smalling RW, Nishikawa A, Merhige ME. Assessment of coronary artery disease severity by PET: comparison with quantitative arteriography in 193 patients. Circulation 1989;79:825-35.

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Health Care Inspectorate - Pharmaceutical Affairs and Medical Technology

CERTIFICATE NUMBER: *NL/H 15/1005215*

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended
Art. 15 of Directive 2001/20/EC

The competent authority of Netherlands confirms the following:
The manufacturer: ***Cyclotron MCA B.V.***
Site address: ***Wilhelminalaan 12, ALKMAAR, 1815JD, Netherlands***

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ***6766 F*** in accordance with Art. 40 of Directive 2001/83/EC and Art. 13 of Directive 2001/20/EC transposed in the following national legislation:
Art. 100 of the Medicines Act
Art. 100 of the Medicines Act

Other :
.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-11-03*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

---

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Doc. 6

Part 2

Human Medicinal Products Human Investigational Medicinal Products

1 MANUFACTURING OPERATIONS	
1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.4 Small volume liquids Special Requirements 5 Radiopharmaceuticals
	1.1.3 Batch certification
1.5	**Packaging**
	1.5.2 Secondary packing
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical*

Manufacture of active substance. Names of substances subject to inspection :
FLUDEOXYGLUCOSE (18F)(en)

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance : FLUDEOXYGLUCOSE (18F)	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : synthesis by fully automatic and dissolving API *Special Requirements:* 5. Radiopharmaceuticals
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared *Special Requirements:* 5. Radiopharmaceuticals
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : diluting to the desired radioactive concentration *Special Requirements:* 5. Radiopharmaceuticals 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) *Special Requirements:* 5. Radiopharmaceuticals

Doc. 6

	3.5.3 Secondary Packaging (placing th[redacted] primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance) *Special Requirements:* 5. Radiopharmaceuticals
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing *Special Requirements:* 5. Radiopharmaceuticals 3.6.3 Microbiological testing including sterility testing *Special Requirements:* 5. Radiopharmaceuticals

2016-12-13

Name and signature of the authorised person of the Competent Authority of Netherlands

[redacted]

Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport
rijksoverheid rijksoverheid rijksoverheid

Drs
Health Care Inspectorate - Pharmaceutical Affairs and Medical Technology
Tel: *+31 88 1205000*
Fax: *+31 88 1205001*

Doc. 7

Noordwest Ziekenhuisgroep

nucleaire geneeskunde
072-548 3480

weigeringsgrond 10.1.c./10.2.g., tenzij anders aangegeven

Aan: IGZ, meldpunt@igz.nl

nucleair geneeskundigen
[redacted]

10.2.e.

Radiofarmacie
[redacted]

Klinische fysica
[redacted]

10.2.e.

Management
[redacted]

Datum 23-02-2017

Betreft: aanvrage toestemming afleveren niet-geregistreerde geneesmiddel ^{13}N-Ammonia

Onderbouwing afwezigheid adequaat medicamenteus alternatief

Korte inleiding:

^{13}N-Ammonia is voor het eerst geproduceerd in 1934 en is daarmee van alle PET tracers veruit de oudste. Deze 'synthese' had echter alleen theoretisch belang en had uiteraard niet tot doel om een PET tracer te produceren, gegeven het feit dat de ontdekking van positron emissie als beeldvormende modaliteit nog bijna 20 jaar op zich zou laten wachten. De eerste experimentele klinische toepassing vond ^{13}N-ammonia in 1972, voor het in beeld brengen van het myocard. Sedert die eerste toepassing is deze tracer eigenlijk altijd hoofdzakelijk gebruikt voor myocardiale diagnostiek. De waarde ervan werd al snel erkend vanuit de kennis dat NH_3 zeer snel en vrijwel volledig door myocardcellen aan de circulatie wordt onttrokken.

In de loop der tijd zijn voor ^{13}N-ammonia [redacted]

Voor wat betreft de motivatie voor het gebruik van ^{13}N-NH_3 voor myocardiale diagnostiek kan het volgende gezegd worden. [redacted]

Doc. 7

[redacted]

[redacted] Zoals boven al aangegeven, het gaat hier om de indicatie: detectie van myocardiale perfusiestoornissen.

Product informatie:
^{13}N-ammonia wordt [redacted]

Doc. 7

[redacted]

[redacted]

Met vriendelijke groet,

[redacted]

Apotheker [redacted]

10.2.e.

[redacted]

Nucleair Geneeskundige

Bijlagen:

- [redacted]

U bent:	Een fabrikant

Doc. 8

Gegevens verzoeker:	
Naam:	[redacted]
Naam fabrikant:	Cyclotron MCA BV
Adres:	Wilhelminalaan 12
Postcode:	1815 JD
Plaats:	Alkmaar
E-mailadres:	[redacted]@nwz.nl
Vestigingsnummer	[redacted]
Wat is uw vergunningnummer?	6766 F

U wilt het volgende:	Ik wil een ongeregistreerd geneesmiddel afleveren.

Wij vragen u om de volgende documentatie bij de hand te hebben (digitaal), om te toetsen of uw verzoek voldoet aan de regels uit artikel 3.17 Regeling Geneesmiddelenwet:

1. Ingevulde en ondertekende artsenverklaring.
2. Onderbouwing van de afwezigheid van een adequaat medicamenteus alternatief.
3. Informatie over het product, zoals een bijsluiter of een Summary of Product Characteristics (SPC) (ofwel de IB1-tekst). Als de bijsluiter of SPC van het product niet in het Nederlands, Engels of Duits beschikbaar is, moet u van het betreffende document een Nederlandse of Engelse vertaling mee sturen.
4. Een verklaring waaruit blijkt dat het geneesmiddel onder GMP omstandigheden is gemaakt:
   - Als de vrijgifte fabrikant in de EER gevestigd is of in een land waarmee de EU een Mutual Recognition Agreement (MRA) heeft en het geneesmiddel is in dat land geregistreerd, opgave van naam en adres van de fabrikant (of een kopie van de farikantenvergunning).
   - Als de fabrikant buiten de EER (de EU lidstaten + IJsland, Noorwegen en Liechtenstein) is gevestigd of niet in een land waarmee de EU een MRA heeft, een geldig GMP certificaat uitgegeven door een bevoegde EU autoriteit of een 'certificate of a pharmaceutical product' afgegeven door het land van herkomst.
5. Een verklaring dat alle geconstateerde bijwerkingen worden bijgehouden(farmacovigilantieverklaring).

Aan het einde van dit digitale formulier kunt u bovenstaande documentatie uploaden.

Het geneesmiddel valt onder de Opiumwet.	Nee

Het geneesmiddel is een vaccin of bloedproduct.	Nee

Het afleveren van het geneesmiddel op artsenverklaring:	
Merknaam of code:	13N-Ammonia in spuit
Werkzaam bestanddeel:	13N-Ammonia
Sterkte:	300 of 400 MBq
Farmaceutische vorm:	oplossing voor IV injectie
In de (handels)verpakking voor (land):	Nederland
De fabrikant verantwoordelijk voor de vrijgifte is gevestigd in: *NB. De fabrikant kan een andere firma zijn dan de registratiehouder*	Nederland

** EER = Europese Economische Ruimte; de EU lidstaten + IJsland, Noorwegen en Liechtenstein*

DOC. 8

Vul hieronder de volgende gegevens in van de fabrikant:	
Naam Fabrikant:	Cyclotron MCA BV
Adres:	Alkmaar
Land:	Nederland

Maak uw keuze uit de volgende situaties:	Het geneesmiddel heeft een handelsvergunning buiten de EER.

Het geneesmiddel is geregistreerd in:	Verenigde Staten
Het geneesmiddel is geregistreerd onder het nummer:	onbekend

Mijn patiënt kan niet adequaat worden behandeld met in Nederland in de handel toegelaten geneesmiddel(en) en ik wens derhalve voor de behandeling van mijn patiënt(en) te beschikken over het geneesmiddel voor de indicatie.

Naam indicatie:	detectie myocardiale perfusiestoornissen

Dit is het eerste verzoek voor toestemming. Ik voeg als bijlagen toe:

o Ingevulde en ondergetekende artsenverklaring. *Deze kunt u aan het einde van het formulier uploaden.*

o Informatie over het product, zoals bijvoorbeeld een bijsluiter of een SPC (Summary of Product Characteristics ofwel de IB1- tekst). *Deze kunt u aan het einde van het formulier uploaden.*

o Een verklaring dat alle geconstateerde bijwerkingen zullen worden vastgelegd (Farmacovigilantieverklaring). *Deze kunt u aan het einde van het formulier uploaden.*

Onderbouwing van de afwezigheid van een adequaat medicamenteus alternatief. Om invulling van deze voorwaarde te controleren, bekijkt IGZ de indicatie waarvoor het ongeregistreerde geneesmiddel wordt toegepast. Deze onderbouwing bestaat uit een overzicht waaruit blijkt met welke in Nederland geregistreerde geneesmiddelen de indicatie behandeld kan worden en de reden waarom deze geneesmiddelen in dit geval niet gebruikt kunnen worden.

zie bijgevoegde brief Motivatie gebruik 13N-NH3 & Productinformatie

U kunt hieronder uw onderbouwing typen. Let op dit tekstveld is gelimiteerd tot 400 woorden: *

** Indien u een tekst/bijlage wenst te sturen van bijvoorbeeld de onderbouwing van de arts, kunt u deze kunt u aan het einde van het formulier uploaden.*

De Inspectie voor de Gezondheidszorg heeft een wettelijke termijn van maximaal acht weken voor het behandelen van uw verzoek om toestemming voor het leveren van een niet-geregistreerd geneesmiddel op artsenverklaring, maar streeft ernaar uw verzoek zo spoedig mogelijk af te handelen. Indien het niet-geregistreerd geneesmiddel op zeer korte termijn moet worden toegediend of verstrekt, dient u de urgentie hiervan aan te geven in dit formulier via het beantwoorden van de volgende vraag:

Betreft het een patiënt aan wie gezien de klinische situatie het niet-geregistreerd geneesmiddel op de zeer korte termijn moet worden toegediend of worden verstrekt?	Nee

U heeft de volgende bestanden geupload:
..\4689\13N-NH3 & 15O-H2O-guidelines NVNG.pdf
..\4689\Artsenverklaring 13N-NH3.pdf
..\4689\Farmacovigilantieverklaring 13N-NH3.pdf
..\4689\FDA Review 13N-NH3-1999.pdf
..\4689\GMP certificaat 2016.pdf
..\4689\Motivatie gebruik 13N-NH3 & Productinformatie.pdf

U bent aan het einde van het digitaal formulier geneesmiddelen zonder handelsvergunning gekomen.

Indien u een afdruk wilt van de ingevulde vragenlijst, dan kunt u nu rechts bovenaan de pagina op "Gegeven antwoorden afdrukken" klikken.
Als u het printbestand digitaal op wilt slaan dan kunt u het bestand met behulp van een pdf-printer tot een digitaal pdf bestand omzetten.

Doc. 8

*Aangezien u vertrouwelijke informatie heeft ingevuld kunnen we u het ingevulde formulier **niet** per e-mail toesturen.*

Door onderstaand vakje aan te vinken geeft u aan dat het formulier waarheidsgetrouw is ingevuld:	Ik verklaar dit digitaal formulier naar waarheid te hebben ingevuld.
Naam verzoeker:	[redacted]
Geslacht verzoeker:	[redacted]
Functie	Apotheker[redacted]
Plaats:	Alkmaar
Datum: (dd-mm-jjjj)	24-2-2017
E-mailadres verzoeker:	[redacted]@nwz.nl
Telefoonnummer verzoeker:	[redacted]

U dient uw aanvraag in door op de knop "Versturen" te klikken.

weigeringsgrond 10.2.e.

Doc. 9.

Van: meldpunt@igz.nl
Aan: _Dienstpostbus IGZ Utrecht
Onderwerp: 1702 4539, Nieuwe aanvraag Geneesmiddelen zonder Handelsvergunning (GZH) - Referentienummer
Datum: vrijdag 24 februari 2017 11:36:51
Bijlagen: Nieuwe aanvraag Geneesmiddelen zonder Handelsvergunning (GZH) - Referentienummer [redacted]
13N-NH3 & 15O-H2O-guidelines NVNG.pdf
Artsenverklaring 13N-NH3.pdf
Farmacovigilantieverklaring 13N-NH3.pdf
FDA Review 13N-NH3-1999.pdf
GMP certificaat 2016.pdf
Motivatie gebruik 13N-NH3 & Productinformatie.pdf
IGZ_GZH_P2014_report[redacted].

Bijgaand bericht inboeken svp.

Nieuwe melding Afdeling Meldpunt - team farmaceutische bedrijven

Met vriendelijke groet,

[redacted]<meldpunt@igz.nl>

24-02-2017 09:40 _dienstpostbus IGZ meldpunt,: Date sent: Feb 24, 2017 9:39 AM
To: meldpunt@igz nl
Subject: Nieuwe aanvraag Geneesmiddelen zonder Handelsvergunning (GZH) - Referentienummer: IGZ_GZH_4689

Nieuw digitaal formulier geneesmiddelen zonder handelsvergunning
Referentienummer IGZ_GZH_4689
Ontvangen op vrijdag 24 februari 2017 9:39:08
Vanaf 1 februari 2016 geldt bij IGZ legitimatieplicht voor bezoekers. Rijkspas, paspoort, identiteitskaart of rijbewijs worden als geldige legitimatie beschouwd.

Sinds 1 januari 2016 is het postadres van de Inspectie voor de Gezondheidszorg gewijzigd in: Postbus 2518 ? 6401 DA Heerlen.
Vanaf 1 februari 2016 geldt bij IGZ legitimatieplicht voor bezoekers. Rijkspas, paspoort, identiteitskaart of rijbewijs worden als geldige legitimatie beschouwd.

Sinds 1 januari 2016 is het postadres van de Inspectie voor de Gezondheidszorg gewijzigd in: Postbus 2518 – 6401 DA Heerlen.

Cyclotron MCA BV 13N-Ammonia in spui13N-Ammonia 300 of 400 MBq 3.17 aanvraag, WPM-nummer IT: [redacted] d.d. 24-02-2017

Hoog risico aanvraag

1. Aanvrager (in NL gevestigd):

   Cyclotron MCA BV
   [redacted], apotheker [redacted]
   Wilhelminalaan 12
   1815 JD Alkmaar

(Adresgegevens volledig en aanvrager Is een bevoegde fabrikant vergunningnr 6766F?: akkoord)

2. (Geneesmiddel (handelsnaam, stofnaam, sterkte): 13N-Ammonia in spuit 13N-Ammonia300 of 400 MBq
   (gegevens volledig?: akkoord

3. Farmaceutische vorm: oplossing voor IV injectie
   (gegevens volledig en consistent?: akkoord

4. Indicatie: detectie myocardiale perfusiestoornissen

Op de artsenverklaring staat myocardiale perfusie stoornissen
(indicatie op aanvraag en op artsenverklaring komen overeen?: akkoord

5. Naam en adres fabrikant:

Naam Fabrikant: Cyclotron MCA BV
Adres: Alkmaar
Land: Nederland

(adresgegevens fabrikant compleet?: akkoord

6. Land waar geneesmiddel is geregistreerd: Op het aanvraagformulier is het volgende aangegeven:

Het geneesmiddel is geregistreerd in: Verenigde Staten
Het geneesmiddel is geregistreerd onder het nummer: onbekend

Het product waarvoor nu een aanvraag is ingediend van Cyclotron is nergens geregistreerd en wordt geproduceerd door Cyclotron zelf.

(volgens aanvraagformulier geregistreerd in....?Voor de aangevraagde indicatie? : akkoord

7. Artsenverklaring: d.d.22-02-2017, [redacted], Nucleair Geneeskundige voor patiënt met code [redacted]

Arts is BIG geregistreerd onder nummer [redacted]

(conform F039, ondertekend en compleet?: akkoord

Doc. 11

8. Aanmeldingsformulier: d.d. 24-02-2017, naar waarheid ingevuld door [redacted], apotheker [redacted]
(betreft eerste aanmelding,
product is niet geregistreerd (komt niet voor in CBG databank)
product komt niet in aanmerking voor com use CBG; er loopt nl nog geen registratieprocedure
product is niet bestemd voor gebruik in klinisch onderzoek
aanvraag is ondertekend en compleet?: akkoord

9. Productinformatie:

Onderstaande is als productinformatie bijgevoegd

Product informatie:

[redacted]

10.1.c./10.2.g.

Met vriendelijke groet,

[redacted]

Apotheker [redacted]

[redacted]

Nucleair Geneeskundige

(er is een productdossier IDB/IMPD/SPC/bijsluiter bijgevoegd?: akkoord

10. Onderbouwing noodzaak tot gebruik ongeregistreerd geneesmiddel/lijst van geregistreerde geneesmiddelen bij CBG of EMA die niet gebruikt kunnen worden voor behandeling van genoemde indicatie :

Doc. 11

Noordwest Ziekenhuisgroep
nuclealre geneeskunde
072-548 3480

nucleair geneeskundigen
[redacted]

Aan: IGZ, meldpunt@igz.nl

Radiofarmacie
[redacted]

Klinische fysica
[redacted]

Datum 23-02-2017

Management
[redacted]

Betreft: aanvraag toestemming afleveren niet-geregistreerde geneesmiddel ^{13}N-Ammonia

Onderbouwing afwezigheid adequaat medicamenteus alternatief

Korte inleiding:
^{13}N-Ammonia is voor het eerst geproduceerd in 1934 en is daarmee van alle PET tracers veruit de oudste. Deze 'synthese' had echter alleen theoretisch belang en had uiteraard niet tot doel om een PET tracer te produceren, gegeven het feit dat de ontdekking van positron emissie als beeldvormende modaliteit nog bijna 20 jaar op zich zou laten wachten. De eerste experimentele klinische toepassing vond ^{13}N-ammonia in 1972, voor het in beeld brengen van het myocard. Sedert die eerste toepassing is deze tracer eigenlijk altijd hoofdzakelijk gebruikt voor myocardiale diagnostiek. De waarde ervan werd al snel erkend vanuit de kennis dat NH_3 zeer snel en vrijwel volledig door myocardcellen aan de circulatie wordt onttrokken.
In de loop der tijd zijn voor ^{13}N-ammonia [redacted]

[redacted]

10.1.c./10.2.g.

Voor wat betreft de motivatie voor het gebruik van ^{13}N-NH_3 voor myocardiale diagnostiek kan het volgende gezegd worden [redacted]

[redacted]

[redacted]

10.1.c./10.2.g.

Doc. 11

[redacted]

[redacted] Zoals boven al aangegeven, het gaat hier om de indicatie: detectie van myocardiale perfusiestoornissen.

10.1.c./10.2.g.

Product informatie:

[redacted]

Met vriendelijke groet,

[redacted]

Apotheker [redacted]

[redacted]

Nucleair Geneeskundige

Doc. 11

Met vriendelijke groet,

[redacted]

Apotheker [redacted]

[redacted]

Nucleair Geneeskundige

Bijlagen:

- FDA: Medical and Statistical Review of N-13 Ammonia Positron Emission Tomography - August 9, 1999
- Hoofdstuk "^{13}N-ammonia and H2 15O PET/CT of Myocardial Perfusion" uit 2016 editie Richtlijnen Nederlandse Vereniging van Nucleaire Geneeskunde.

3

Wetenschappelijk artikelen:

- 13N-ammonia and FI2150 PET/CT of Myocardial Perfusion
- FDA Review 13N-NH3-1999

(onderbouwing voor gebruik is beschreven in de productinformatie? Onderbouwing afwezigheid medicamenteus alternatief is bijgevoegd? akkoord

11. Verklaring van GMP-omstandigheden: GMP certificaat Cyclotron MCA B.V. d.d. 13-12-2016
(Geneesmiddel bereid onder GMP-omstandigheden? Indien van toepassing check MRA-status op: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/mutual_recognition_agreements.jsp&mid=WC0b01ac058006e013*:* akkoord

12. Farmacovigilantieverklaring: d.d. 24-02-2016 ondertekend door [redacted], apotheker [redacted]
(verklaring volledig en correct?: akkoord

Aanvullende/beperkende voorwaarden noodzakelijk: nee

Eindconclusie d.d. 11-4-2017:
Toestemming kan worden gegeven om 13N-Ammonia, 300 of 400 MBq in spuit, oplossing voor IV injectie, afkomstig uit Nederland, op artsenverklaring af te leveren voor de indicatie 'detectie myocardiale perfusiestoornissen'. De toestemming is geldig voor één jaar.

Documenten die zijn beoordeeld

Documentnaam	**Datum en zo nodig nadere omschrijving document**
Formulier verzoek om toestemming	d.d. 24-02-2017, naar waarheid ingevuld door [redacted], apotheker [redacted]
Artsenverklaring	d.d.22-02-2017, [redacted], Nucleair Geneeskundige voor patiënt met code [redacted]
Motivering afwezigheid adequaat medicamenteus alternatief	Bijlage brief NoordWest Ziekenhuisgroep d.d. 23-02-2017 van [redacted], apotheker en [redacted], Nucleair Geneeskundige
Productinformatie	Bijlage brief NoordWest Ziekenhuisgroep

Doc. H

	d.d. 23-02-2017 van [redacted], apotheker en [redacted], Nucleair Geneeskundige
Eventueel aanvullende productinformatie	
Verklaring dat het geneesmiddel onder GMP-omstandigheden is gemaakt	GMP certificaat Cyclotron MCA B.V. d.d. 13-12-2016
Farmacovigilantieverklaring	d.d. 24-02-2016 ondertekend door [redacted], apotheker [redacted]
Eventueel literatuur als achtergrond	- 13N-ammonia and FI2150 PET/CT of Myocardial Perfusion - Bijlage FDA Review 13N-NH3-1999
Aanvullende informatie	

Naam beoordelaar: [redacted]
Datum: 29-03-2017
Bestede tijd: 40 min

Naam peer reviewer: [redacted]
Datum: 11-04-2017
Bestede tijd: 90 min

Doc. 13

^{13}N-ammonia and $H_2{}^{15}O$ PET/CT of Myocardial Perfusion

P. Raijmakers, VUmc Amsterdam

1. Introduction

Coronary artery disease (CAD) is a major cause of death in the modern world. The diagnosis of CAD is mainly focused on the detection of obstructive epicardial coronary stenosis. Positron emission tomography (PET) is widely accepted as a diagnostic technique which can be used to assess myocardial perfusion. Three PET tracers have been validated (Table 1) for assessing myocardial perfusion. $H_2{}^{15}O$ is characterized by different kinetic properties as compared with $^{13}NH_3$, and ^{82}Rb. The latter tracers become metabolically trapped while cleared from the intravascular compartment, yielding excellent qualitatively gradable imaging due to high tissue-to-background ratios. In contrast, $H_2{}^{15}O$ is a freely diffusible, metabolically inert tracer that promptly reaches equilibrium between blood and tissue, thus is not accumulated in the myocardium. As a consequence, direct radiotracer distribution images of $H_2{}^{15}O$ are of little diagnostic value. In recent years, however, improved techniques and parametric imaging by automated software packages, have generated qualitatively gradable $H_2{}^{15}O$ perfusion images comparable to $^{13}NH_3$, and ^{82}Rb. Meta-analyses comparing myocardial PET to SPECT and cardiovascular magnetic resonance imaging (CMR),demonstrate that MPI with PET yields the highest diagnostic accuracy. The majority of clinical studies on the diagnostic accuracy of detection of obstructive CAD have been conducted with static uptake images of ^{82}Rb and $^{13}NH_3$. Weighted sensitivity, specificity, NPV, and PPV were 91, 86, 81, and 93%, respectively. Furthermore, cardiac PET imaging can potentially be used to study subendocardial perfusion. Myocardial ischaemia occurs principally in the subendocardial layer, whereas conventional myocardial perfusion imaging provides no information on the transmural myocardial blood flow (MBF). In a recent $H_2{}^{15}O$ PET study a significantly decreased subendocardial MBF was found in ischaemic myocardium.

Table 1. Characteristics of $H_2{}^{15}O$, $^{13}NH_3$, and ^{82}Rb for PET myocardial perfusion imaging.

	$H_2{}^{15}O$	$^{13}NH_3$	^{82}Rb	Comment
Half-life	123 sec	9,97 min	76 sec	Mandatory on-site production of the tracers given their short physical half-life

DOC. 13

Production	Cyclotron	Cyclotron	Generator	Generator equipment have lower installation and maintenance costs
Kinetics	Freely diffusible, metabolically inert	Metabolically trapped in myocardium	Metabolically trapped in myocardium	Complete extraction from bloodpool into myocardial tissue renders $H_2{}^{15}O$ an ideal perfusion tracer
Mean positron range in tissue	1,1 mm	0,4 mm	2,8 mm	^{82}Rb 's higher tissue penetration depth limits the spatial resolution of the perfusion imaging
Dose	0,00093 mSv/ MBQ	0,002 mSv/ MBq	0,0034 mSv/ MBq	

Quantification of myocardial perfusion with PET

Dynamic PET acquisition protocols allows quantification of stress and rest myocardial blood flow (MBF in units of $mL \cdot min^{-1} \cdot g^{-1}$ and calculation of coronary flow reserve (CFR). Literature suggests that quantitative analysis is superior to static uptake image evaluation. Furthermore, hyperaemic MBF assessment seems to outperform CFR for the diagnosis of obstructive CAD, which may result in stress only protocols. Thresholds for what should be considered pathological hyperaemic MBF or CFR are unfortunately not uniform. MBF is related to age, sex, and cardiovascular risk profile. Perfusion thresholds will be tracer specific and may require correction for individual patient characteristics. Ongoing studies are targeted to addressing these issues. Use of a single cut-off may be a simplification of the underlying pathophysiology, as MBF is determined by the combination of epicardial coronary flow and microvascular vasomotor function. In terms of prognosis, the quantitative nature of PET has shown incremental value. The extent and severity of (reversible) perfusion defects diagnosed with PET holds strong prognostic information beyond traditional cardiovascular risk factors. Of particular interest is the fact that apparently normal perfusion images with a homogenous tracer distribution can be reclassified based on diffusely abnormal hyperaemic MBF or CFR. Several studies have revealed that this subset of patients is at increased risk for future cardiac events.

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Coronary computed tomography angiography (CCTA)
CCTA is a promising tool for non-invasive evaluation of coronary anatomy. Pooled analysis of the currently available literature demonstrates a high sensitivity (96%) and negative predictive value (NPV, 94%), rendering it a clinically useful tool to rule out obstructive coronary stenosis. However, despite its non-invasive nature and high sensitivity, CCTA is not able to determine the haemodynamic relevance for a given epicardial coronary stenosis. Indeed, several studies have clearly demonstrated the disconcordancy between the anatomical and functional aspects of coronary atherosclerosis, emphasizing the role of myocardial perfusion imaging (MPI) in the non-invasive evaluation of CAD. In recent years there has been a fast evolution of the hybrid imaging technique, incorporating multidectector-row CT with PET detector techniques.

Hybrid Cardiac PET/CT
Hybrid cardiac PET/CT imaging enables the near simultaneous evaluation of coronary anatomy and (quantitative) myocardial perfusion in a single scanning session, which can be performed within 30-60 min. Although the number of diagnostic studies on the accuracy of hybrid cardiac PET/CCTA is small, they demonstrate an improved diagnostic performance as compared with either imaging modality alone. Three studies have evaluated the diagnostic value of hybrid PET/CCTA over stand-alone CCTA and PET MPI. Hybrid imaging is shown to be particularly useful for enhancing specificity and PPV of CCTA, although significant rises in these parameters can also be observed when compared to PET alone.
The hybrid cardiac PET/CT imaging results, generally categorize patients into one of four groups. The first category represents patients with a normal CCTA and a normal MBF/CFR, confirming a normal coronary circulation. Secondly, a normal CCTA combined with a decreased MBF and/or CRF represents coronary microvascular dysfunction. Hence, a completely normal CCTA can rule out epicardial atherosclerotic disease, but may need conformation of normal hyperaemic MBF and CFR to rule out coronary microvascular dysfunction.
An abnormal CCTA, compatible with obstructive CAD, warrants confirmation with perfusion imaging to determine its actual haemodynamic relevance and MPI should act as a gatekeeper for further invasive testing. A third group, representing patients with an abnormal CCTA and a decreased MBF, may benefit from revascularization. Not only the presence of ischaemia, but also the extent of the jeopardized area is important. Revascularization in patients with mild to moderate ischaemic burden (i.e. <10% of the myocardium) does not alter outcome, yet alleviate symptoms. Satisfactorily medically controlled anginal symptoms therefore justify a conservative approach and a potentially hazardous invasive procedure should be deferred. Drug refractory angina and / or large ischaemic burden, seems to warrant revascularisation. This topic is, however, still a matter of debate and further studies are needed. Lastly, patients with an abnormal CCTA and a normal MBF may benefit from optimal medical treatment. With the implementation of cardiac hybrid PET/CT protocols, a more pragmatic referral of patients to the catheterisation laboratory may be achieved, thus minimising the need for invasive diagnostic procedures.

2. Methodology
This review is based on available scientific literature on the subject.

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3. Indications

Hybrid PET/CT:

Evaluation of patients with an intermediate likelihood of CAD, for diagnosis of CAD, including location and severity of CAD and extent of ischaemic area.

Additional indications

Myocardial Perfusion PET:

- Assessment of regional perfusion in the presence of obstructive coronary artery disease

Absolute contraindications for adenosine stress myocardial perfusion imaging with PET:

- Unstable angina/acute coronary syndrome,
- Severe bronchospasms
- Second or third-degree heart block or sick sinus syndrome, without a pacemaker
- Symptomatic aortic stenosis and hypertrophic obstructive cardiomyopathy
- Systolic blood pressure <90 mmHg
- Cerebral ischaemia
- Persantin/dipyridamol use in the 24 h before adenosine stress test

Relative contraindications to vasodilator stress tests are:

- Severe sinus bradycardia (heart rate <40/min)
- Severe atherosclerotic laesions of extracranial artery

4. Relation to other diagnostic procedures/therapies

Several techniques can be used to evaluate CAD, including CCTA, cardiac MRI, myocardial SPECT and stress echocardiography. Owing to the quantitative nature, routine use of attenuation correction, higher spatial resolution, shorter study protocols, and lower radiation exposure, cardiac PET surpasses SPECT MPI both in terms of diagnostic accuracy and patient convenience. However, comprehensive 'head to head' studies comparing diagnostic accuracy of imaging techniques regarding the detection of CAD and abnormal MBF are scarce. More clinical research is needed regarding efficient diagnostic strategies for detection of obstructive CAD. Furthermore, there are three PET perfusion tracers available for myocardial perfusion imaging: $^{13}NH_3$, $H_2{}^{15}O$ and ^{82}Rb. These are all short-lived tracers that require on-site production. ^{82}Rb has the advantage of being generator produced, avoiding the need for an on-site cyclotron. However, ^{82}Rb's longer positron range and lower count statistics due to the ultra-short half-life (76 sec) compromise image resolution (see also table 1 for comparison of the PET tracers).

5. Medical information necessary for planning

- Information which should be available prior to planning of the procedure:
- Indication for diagnostic cardiac PET and/or CT
- body mass
- ability to lie still for approximately 45 min (in case of $H_2{}^{15}O$ PET/CT procedure)
- presence of metallic implants
- renal function
- allergy to iodinated contrast agents
- heart rhythm

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- (cardiac) medication (interaction with adenosine, preparation before adenosine PET, rhythm control during CCTA)
- contra indications for beta-blocker use
- pulmonary function including presence of COPD/asthma
- clinical instability (recent myocardial infarction, decompensated heart failure, hypotension)
- informed consent

6. Radiopharmaceutical

Tracer:	$H_2{}^{15}O$
Activity:	370 MBq (for PET detection in 3 dimensional mode) (dose depends upon characteristics of PET imaging system, above mentioned dose is for 3D mode)
Administration:	Intravenous injection, bolus

Alternatively:

Tracer:	^{13}N-ammonia
Activity:	370-925 MBq (dose depends upon characteristics of PET system, e.g. 2D-3 D mode, crystal)
Administration:	Intravenous injection, bolus or <30 sec of infusion

7. Radiation safety

Pregnancy is a contraindication for cardiac PET/CT procedure

Lactation:

Due to the short half time of ^{15}O /^{13}N-ammonia only a short interruption of lactation is required

Radiation exposure:

$H_2{}^{15}O$: 0,00093 mSv/MBQ

^{13}N-ammonia: 0,0034 mSv/MBq

8. Patient preparation/essentials for procedure

- Refrain from intake of products containing caffeine or xanthine 24 h prior to the scan. This includes beverages such as cola, coffee, tea, energy drinks, foods such as chocolate and medication including anaelgesia containing caffeine.
- Dipyridamol/ Persantin should be stopped 24 h prior to adenosine infusion.
- Cardiac medication which may interfere with the stress test (eg adenosine) should be stopped termporarily. The decision to interrupt cardiac medication should be left to the referring physician. Interruption should ideally be five pharmacological half-lives of relevant drug. This applies for nitrates, but may also apply for beta-blockers and calcium antagonists.
- Severe COPD : consider an alternative stress test.
- The patient should be haemodynamically stable for >48 h prior to the stress test.
- Additional preparation: ECG monitoring, blood pressure monitoring

9. Acquisition and processing

Rest/ stress myocardial $H_2{}^{15}O$ -PET/CT imaging protocol:

- Scout CT for patient positioning

- Two min after starting the intravenous adenosine infusion 140 µg. kg^{-1}. min^{-1}: 370 MBq of $H_2{}^{15}O$ injection as a 5 mL (0,8 $ml.s^{-1}$) bolus, immediately followed by a 35 ml saline flush (2 $ml.\ s^{-1}$).

A 6-min PET scan starts simultaneously with the administration of $H_2{}^{15}O$.
This dynamic scan sequence is immediately followed by a respiration-averaged low dose CT scan (LD-CT) to correct for attenuation (55 mAs; rotation time, 1,5 sec; pitch, 0,825; collimation, 16 · 0,625; acquiring 20 cm in 37 sec) during normal breathing.
The adenosine infusion is terminated after the LD-CT.
After an interval of 10 min, to allow for decay of radioactivity and washout of adenosine, an identical rest PET sequence can be performed under resting conditions. There is evidence supporting stress MBF only protocols, therefore the rest MBF PET study is optional.
Image reconstruction: 3D row action maximum likelihood algorithm of 22 frames (1x10, 8x5, x 10,x15, 3x20, 2x30, and 2x60 seconds), including all appropriate corrections.
Parametric MBF images are generated and quantitative analysis can be performed using specifically developed software, Cardiac VUer. Other software packages such as Carimas are available, and yield comparable quantitative results. MBF is expressed in $mL \cdot min^{-1} \cdot g^{-1}$ of perfusable myocardium and is analysed according to the 17-segment model of the American Heart Association (AHA). Subsequently, MBF is calculated for each of the three vascular territories (right coronary artery [RCA], left anterior descending artery [LAD], and circumflex artery [CX]). The coronary flow reserve (CFR) is defined as the ratio between stress (hyperaemic) and rest (baseline) MBF.

10. Interpretation

The image analysis is performed on both global left ventricular uptake and on a per-vessel basis.
Additionally, a semi-quantitative approach can be used. Myocardial perfusion PET images are divided into 17 segments (AHA model), and each segment is scored using a 5 point scale ranging from 0 (normal perfusion), 1 (mildly reduced perfusion), 2 (moderately reduced perfusion), 3 (severely reduced perfusion), to 4 (absent perfusion). This yields a summed perfusion score for both stress and rest myocardial perfusion images.
After gated acquisition, LV parameters including LV volumes and EF can be used for the overall interpretation.
Quantitative analysis adds information to static uptake image grading. Reported thresholds of what should be considered pathologically decreased stress MBF or CFR are not consistent. Hence, different thresholds should be used for the different PET tracers.
The optimal cut-off value for detecting flow-limiting stenosis of coronary arteries by means of $H_2{}^{15}O$ PET hyperaemic MBF is ≤ 2,3 $ml \cdot min^{-1} \cdot g^{-1}$ and that for CFR is ≤ 2,5.
In addition, hyperaemic MBF assessment seems to outperform CFR in the diagnosis of obstructive CAD, enabling stress only PET protocols offering a further reduction of PET imaging time.

The hybrid cardiac PET/CT imaging results generally categorise patients into one of four groups:

1. patients with a normal CCTA and normal MBF/CFR, confirming normal coronary circulation.

2. patients with a normal CCTA combined with decreased MBF and/or CRF, indicating coronary microvascular dysfunction
3. patients with an abnormal CCTA and decreased MBF/CFR , indicating vessels with significant stenosis of the coronary arteries.
4. patients with an abnormal CCTA and normal MBF, indicating vessel(s) with non-significant stenosis of coronary arteries.

11. Report

Patient-specific information

- Relevant history, current medication
- Indication for the study
- Type of study (radiopharmaceuticals, acquisition protocol, type of metabolic preparation), haemodynamics and ECG
- Image description (visual, semi-quantitative, quantitative evaluation)
- Quantitative data, including rest MBF, stress MBF, Coronary Flow Reserve, preferably for the three coronary territories (LAD, RCA and CX)
- For hybrid PET/CCTA: correlation between MBF and the main findings of the CCTA (e.g. location of significant coronary obstructive disease and downstream MBF)
- For gated acquisition: LV volumes, EF and wall motion abnormalities
- Conclusion

12. Literature

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Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport

Artsenverklaring

bestemd om te overleggen aan de fabrikant, groothandelaar of apotheekhoudende voor het afleveren van een geneesmiddel waarvoor geen vergunning voor het in de handel brengen in Nederland is verleend.

Deze verklaring is tot één jaar na dagtekening geldig.

Ondergetekende,

Naam en voorletter(s) arts [redacted]

Specialisme, indien van | Nucleair Geneeskundige

BIG registratienummer arts [redacted]

Werkadres | Wilhelminalaan 12

Postcode en plaats | Postcode 1815 JD | Plaats Alkmaar

Telefoonnummer [redacted]

Verklaart hierbij

a) dat zijn/haar patiënt(e),

Codenummer [redacted]

lijdende aan

myocardiale perfusie stoornissen,

niet adequaat kan worden behandeld met in Nederland in de handel toegelaten geneesmiddelen en hij/zij
derhalve voor de behandeling van zijn/haar patiënt(en) wenst te beschikken over het geneesmiddel

Naam geneesmiddel en | 13N-NH3 per spuit.

b) dat hij/zij zich ervan bewust is dat voor het af te leveren geneesmiddel geen vergunning voor het in de handel brengen in Nederland is verleend, en derhalve in Nederland niet is getoetst aan criteria betreffende werkzaamheid, schadelijkheid en deugdelijkheid zoals gesteld in de Geneesmiddelenwet en dat hij/zij zijn/haar patiënt(en) of diens wettelijke vertegenwoordiger nadrukkelijk daarop heeft gewezen.
c) dat hij/zij de volle verantwoordelijkheid draagt en het risico aanvaardt voor de behandeling van zijn/haar patiënt(en) met dit geneesmiddel.
d) dat hij/zij alle hem/haar bekend geworden ziekteverschijnselen die ontstaan tijdens de behandeling en waarbij het vermoeden bestaat dat het geneesmiddel de oorzaak is, zal melden aan de Inspectie voor de Gezondheidszorg; dat hij/zij dit op geanonimiseerde wijze zal melden, zodanig dat de privacy van de betrokken patiënt zal zijn gewaarborgd.

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Plaats
Alkmaar

Handtekening en datum [redacted]

Dag Maand Jaar
22-02-17

Cyclotron MCA BV, 13N-Ammonia, Regeling Geneesmiddelenwet art 3.17 verlengingsverzoek, [redacted], 13-04-2018, [redacted]

Risico niveau: HOOG, omdat de aanvrager heeft aangegeven dat het niet medisch noodzakelijk is dat de patiënt wordt doorbehandeld. Dit antwoord klopt omdat de patiënten dit middel 1 keer krijgen toegediend voor de diagnose van een aandoening. Aanvraag is eigenlijk niet hoog risico.

Vereiste gegevens

1. **Gegevens aanvrager (in NL gevestigd):**

   Besluit voor fabrikant/groothandel
   Aanvrager en functie: [redacted], apotheker [redacted]
   Naam fabrikant/groothandel: Cyclotron MCA BV
   Vergunning fabrikant/groothandel: 6766 F
   Gecontroleerd in: eudra

   Brief moet gericht worden aan naam instelling:
   Cyclotron MCA BV
   T.a.v. [redacted], apotheker [redacted]
   Wilhelminalaan 12
   1815 JD Alkmaar

   ☒ bevoegde aanvrager

2. **Vorig besluit:**
   Datum eerder besluit: d.d. 20-04-2017
   Kenmerk van de brief met het besluit: 2017-1402314
   Productieland geneesmiddel: Het product waarvoor nu een aanvraag is ingediend van Cyclotron is nergens geregistreerd en wordt geproduceerd door Cyclotron zelf. Besluit afgegeven op: indicatie niveau

3. **Geneesmiddel:**

   13N-Ammonia. 300-400 MBq

   In vorig besluit: 13N-Ammonia in spuit 13N-Ammonia300 of 400 MBq

   ☐ gegevens zijn afwijkend, maar lijken gelijk

4. **Farmaceutische vorm:**

   Oplossing voor injectie in voorgevulde spuit

   Vorig besluit: oplossing voor IV injectie

   ☒ akkoord, gegevens komen overeen met het vorig besluit

5. **Indicatie:**
   (detectie) van myocardiale perfusiestoornissen

   ☒ akkoord, gegevens komen overeen met het vorig besluit

6. **Controle registratie CBG**

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☐ akkoord, geneesmiddel is niet geregistreerd bij het CBG

7. Ontwikkelingen met betrekking tot het niet-geregistreerde geneesmiddel

☒ er zijn geen nieuwe ontwikkelingen; eventueel meegestuurde documenten hoeven niet beoordeeld te worden.
☐ er is sprake van nieuwe ontwikkelingen;

- **Wetenschappelijke artikel(en)**
  «document naam»

  ☐ inhoudelijk niet door meldpunt te beoordelen, voorleggen bij [redacted]
  ☐ akkoord

- **Andere ontwikkelingen?**
  «document naam»

  ☐ inhoudelijk niet door meldpunt te beoordelen, voorleggen bij [redacted]
  ☐ akkoord

Evaluatie documenten:
☐ alles akkoord, voorleggen aan [redacted] niet nodig

8. Artsenverklaring:

☐ niet bijgevoegd

9. Farmacovigilantieverklaring:

☐ wel bijgevoegd, maar behoeft geen beoordeling ten behoeve van toestemming (verlenging)

10. GMP certificaat:

☐ niet bijgevoegd

11. Productinformatie:

☐ niet bijgevoegd

12. Aanvullende informatie:

☐ niet bijgevoegd

10.2.g.

13. Aantal patiënten dat het afgelopen jaar is behandeld: [redacted]

14. Beperkende voorwaarden

☐ akkoord, geen beperkende voorwaarden van toepassing

Tussentijdse conclusie d.d. «datum vandaag»

☐ alles akkoord

Eindconclusie SB 23-05-2018

☐ akkoord, klaar voor gebruik

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De inspectie geeft toestemming aan Cyclotron MCA BV om 13N-Ammonia, 300 of 400 MBq in spuit, oplossing voor IV injectie, afkomstig uit Nederland, op artsenverklaring af te leveren voor de indicatie 'detectie myocardiale perfusiestoornissen'.

De toestemming is geldig voor één jaar na dagtekening van deze brief.
Bij de toetsing van uw aanvraag is de inspectie uitgegaan van de volgende informatie:

Document	Datum en omschrijving
Formulier verzoek om toestemming	d.d. 13-04-2018, naar waarheid ingevuld door [redacted], apotheker
Wetenschappelijke ontwikkelingen	

Naam beoordelaar: [redacted]
Datum: 23-05-2018
Bestede tijd: 30 minuten

Naam peer reviewer: [redacted]
Datum: 23-05-2018
Bestede tijd: 30 min

weigeringsgrond 10.2.e.

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CIBG
Ministerie van Volksgezondheid, Welzijn en Sport

> Retouradres Postbus 16114 2500 BC Den Haag

FABRIKANTENVERGUNNING VAN RADBOUD TRANSLATIONAL MEDICINE B.V., TE NIJMEGEN, VERLEEND PER 1 OKTOBER 2016	
1. REGISTERNUMMER	
6615 F	
2. NAAM, PLAATS EN KVK-DOSSIERNUMMER VERGUNNINGHOUDER	
Radboud Translational Medicine B.V. te NIJMEGEN, 9218811	
3. LOCATIE	
NIJMEGEN	Geert Grooteplein Noord 21, route 142 6525 EZ te NIJMEGEN
4. ADRES VERGUNNINGHOUDER	
Geert Grooteplein Noord 21, route 142 6525 EZ te NIJMEGEN	
5. OMVANG VAN DE VERGUNNING	
Bereidingshandelingen met geneesmiddelen	
Bereidingshandelingen met geneesmiddelen voor onderzoek	
6. WETTELIJKE GRONDSLAG VAN DE VERGUNNING	
Artikel 18, eerste lid, van de Geneesmiddelenwet	
7. BIJLAGEN BIJ DE VERGUNNING	
Bijlage 1, deel 1:	Bereidingshandelingen met geneesmiddelen
Bijlage 1, deel 2:	Invoer van geneesmiddelen
Bijlage 2, deel 1:	Bereidingshandelingen met geneesmiddelen voor onderzoek
Bijlage 2, deel 2:	Invoer van geneesmiddelen voor onderzoek
Bijlage 5:	QP'S
8. ONDERTEKENING	
De Minister van Volksgezondheid, Welzijn en Sport, namens deze, Afdelingshoofd Farmatec [redacted] Dhr. M.J. van de Velde	

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OMVANG VAN DE VERGUNNING MET REGISTERNUMMER 6615 F
adres van de locatie:
Geert Grooteplein Noord 21, r 142 6525 EZ te NIJMEGEN

☒	**GENEESMIDDELEN**
☒	**GENEESMIDDELEN VOOR ONDERZOEK**

TOEGESTANE HANDELINGEN	
☒	**BEREIDINGSHANDELINGEN (CONFORM DEEL 1)**
☐	**INVOER VAN GENEESMIDDELEN (CONFORM DEEL 2)**

BIJLAGE 1 DEEL 1 - BEREIDINGSHANDELINGEN

		Ja	Nee
1.1	STERIELE PRODUCTEN	☒	☐
	1.1.1 Aseptische vervaardiging (van de volgende toedieningsvormen)	☒	☐
	1.1.1.1 Grootvolume vloeistoffen	☐	☒
	1.1.1.2 Gevriesdroogde toedieningsvormen	☐	☒
	1.1.1.3 Halfvaste toedieningsvormen	☐	☒
	1.1.1.4 Kleinvolume vloeistoffen - Radiofarmaceutica	☒	☐
	1.1.1.5 Vaste toedieningsvormen en implantaten	☐	☒
	1.1.1.6 Andere aseptisch vervaardigde producten, namelijk	☐	☒
	1.1.2 Terminale sterilisatie (van de volgende toedieningsvormen)	☐	☒
	1.1.2.1 Grootvolume vloeistoffen	☐	☒
	1.1.2.2 Halfvaste toedieningsvormen	☐	☒
	1.1.2.3 Kleinvolume vloeistoffen	☐	☒
	1.1.2.4 Vaste toedieningsvormen en implantaten	☐	☒
	1.1.2.5 Andere terminaal gesteriliseerde producten, namelijk	☐	☒
	1.1.3 Vrijgifte	☒	☐
1.2	NIET-STERIELE PRODUCTEN	☐	☒
	1.2.1 Niet-steriele producten (bewerkingshandelingen ten a[illegible]n de volgende toedieningsvormen)	☐	☒
	1.2.1.1 Harde capsules	☐	☒
	1.2.1.2 Zachte capsules	☐	☒
	1.2.1.3 Kauwgom	☐	☒
	1.2.1.4 Geïmpregneerde matrices	☐	☒
	1.2.1.5 Vloeistoffen voor uitwendig gebruik	☐	☒

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	1.2.1.6 Vloeistoffen voor inwendig gebruik	☐	☒
	1.2.1.7 Medische gassen	☐	☒
	1.2.1.8 Andere vaste toedieningsvormen	☐	☒
	1.2.1.9 Onder druk staande toedieningsvormen	☐	☒
	1.2.1.10 Radionucleïde generatoren	☐	☒
	1.2.1.11 Halfvaste toedieningsvormen	☐	☒
	1.2.1.12 Zetpillen	☐	☒
	1.2.1.13 Tabletten	☐	☒
	1.2.1.14 Transdermale pleisters	☐	☒
	1.2.1.15 Intraruminaal hulpmiddel	☐	☒
	1.2.1.16 Premixen voor diergeneeskundig gebruik	☐	☒
	1.2.1.17 Andere niet-steriele geneesmiddelen, namelijk	☐	☒
	1.2.2 Vrijgifte	☐	☒
1.3	BIOLOGISCHE GENEESMIDDELEN	☐	☒
	1.3.1 Biologische geneesmiddelen	☐	☒
	1.3.1.1 Bloedproducten	☐	☒
	1.3.1.2 Immunologische producten	☐	☒
	1.3.1.3 Celtherapieproducten	☐	☒
	1.3.1.4 Gentherapieproducten	☐	☒
	1.3.1.5 Biotechnologieproducten	☐	☒
	1.3.1.6 Producten geëxtraheerd uit humaan of dierlijk weefsel	☐	☒
	1.3.1.7 Weefselmanipulatieproducten	☐	☒
	1.3.1.8 Andere biologische geneesmiddelen, namelijk	☐	☒
	1.3.2 Vrijgrifte (lijst van productcategorieën)	☐	☒
	1.3.2.1 Bloedproducten	☐	☒
	1.3.2.2 Immunologische producten	☐	☒
	1.3.2.3 Celtherapieproducten	☐	☒
	1.3.2.4 Gentherapieproducten	☐	☒
	1.3.2.5 Biotechnologieproducten	☐	☒
	1.3.2.6 Producten geëxtraheerd uit humaan of dierlijk w[redacted]	☐	☒
	1.3.2.7 Weefselmanipulatieproducten	☐	☒
	1.3.2.8 Andere biologische geneesmiddelen, namelijk	☐	☒
1.4	ANDERE PRODUCTEN OF BEREIDINGSACTIVITEITEN	☐	☒
	1.4.1 Bereiding van:	☐	☒
	1.4.1.1 Kruidenproducten	☐	☒
	1.4.1.2 Homeopathische producten	☐	☒
	1.4.1.3 Andere, namelijk	☐	☒
	1.4.2 Sterilisatie van werkzame stoffen/tussenproducten/kant-en-klare producten	☐	☒
	1.4.2.1 Filtratie	☐	☒

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	1.4.2.2 Droge hitte	☐	☒
	1.4.2.3 Stoom	☐	☒
	1.4.2.4 Chemisch	☐	☒
	1.4.2.5 Gammastraling	☐	☒
	1.4.2.6 Elektronenbestraling	☐	☒
	1.4.3 Overige	☐	☒
1.5	VERPAKKEN	☒	☐
	1.5.1 Primair verpakken	☐	☒
	1.5.1.1 Harde capsules	☐	☒
	1.5.1.2 Zachte capsules	☐	☒
	1.5.1.3 Kauwgom	☐	☒
	1.5.1.4 Geïmpregneerde matrices	☐	☒
	1.5.1.5 Vloeistoffen voor uitwendig gebruik	☐	☒
	1.5.1.6 Vloeistoffen voor inwendig gebruik	☐	☒
	1.5.1.7 Medische gassen	☐	☒
	1.5.1.8 Andere vaste toedieningsvormen	☐	☒
	1.5.1.9 Onder druk staande toedieningsvormen	☐	☒
	1.5.1.10 Radionucleïde generatoren	☐	☒
	1.5.1.11 Halfvaste toedieningsvormen	☐	☒
	1.5.1.12 Zetpillen	☐	☒
	1.5.1.13 Tabletten	☐	☒
	1.5.1.14 Transdermale pleisters	☐	☒
	1.5.1.15 Intraruminaal hulpmiddel	☐	☒
	1.5.1.16 Premixen voor diergeneeskundig gebruik	☐	☒
	1.5.1.17 Andere niet-steriele geneesmiddelen, namelijk	☐	☒
	1.5.2 Secundair verpakken	☒	☐
1.6	TESTS TEN BEHOEVE VAN KWALITEITSCONTROLE	☒	☐
	1.6.1 Microbiologisch: steriliteitscontrole	☐	☒
	1.6.2 Microbiologisch: anders	☐	☒
	1.6.3 Chemisch/fysisch.	☒	☐
	1.6.4 Biologisch	☐	☒

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Beperkingen of verduidelijkende opmerkingen ten aanzien van de omvang van deze bereidingshandelingen
microbiologie en steriliteitstest zullen worden uitbesteed

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BIJLAGE 1 DEEL 2 - INVOER VAN GENEESMIDDELEN

		Ja	Nee
2.1	**TESTS TEN BEHOEVE VAN KWALITEITSCONTROLE VAN INGEVOERDE GENEESMIDDELEN**	☐	☒
	2.1.1 Microbiologisch: steriliteitscontrole	☐	☒
	2.1.2 Microbiologisch: anders	☐	☒
	2.1.3 Chemisch/fysisch	☐	☒
	2.1.4 Biologisch	☐	☒
2.2	**VRIJGIFTE VAN INGEVOERDE GENEESMIDDELEN**	☐	☒
	2.2.1 Steriele producten	☐	☒
	2.2.1.1 Aseptisch bereid	☐	☒
	2.2.1.2 Terminaal gesteriliseerd	☐	☒
	2.2.2 Niet-steriele producten	☐	☒
	2.2.3 Biologische geneesmiddelen	☐	☒
	2.2.3.1 Bloedproducten	☐	☒
	2.2.3.2 Immunologische producten	☐	☒
	2.2.3.3 Celtherapieproducten	☐	☒
	2.2.3.4 Gentherapieproducten	☐	☒
	2.2.3.5 Biotechnologieproducten	☐	☒
	2.2.3.6 Producten geëxtraheerd uit humaan of dierlijk weefse[redacted]	☐	☒
	2.2.3.7 Weefselmanipulatieproducten	☐	☒
	2.2.3.8 Andere biologische geneesmiddelen, namelijk [redacted]XT. 2016	☐	☒
2.3	**OVERIGE INVOERACTIVITEITEN (ELKE ANDERE RELEVANTE INVOERACTIVITEIT DIE NIET DOOR HET BOVENSTAANDE WORDT BESTREKEN)**	☐	☒
	2.3.1 Locatie van de fysieke invoer	☐	☒
	2.3.2 Invoer van tussenproducten die verdere verwerking zullen ondergaan	☐	☒
	2.3.3 Biologische werkzame stof	☐	☒
	2.3.4 Overige, namelijk	☐	☒

Beperkingen of verduidelijkende opmerkingen ten aanzien van de omvang van deze bereidingshandelingen

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BIJLAGE 2 DEEL 1 - BEREIDINGSHANDELINGEN MET GENEESMIDDELEN VOOR ONDERZOEK

		Ja	Nee
1.1	**STERIELE PRODUCTEN VOOR ONDERZOEK**	☒	☐
	1.1.1 Aseptische vervaardiging (van de volgende toedieningsvormen)	☒	☐
	1.1.1.1 Grootvolume vloeistoffen	☐	☒
	1.1.1.2 Gevriesdroogde toedieningsvormen	☐	☒
	1.1.1.3 Halfvaste toedieningsvormen	☐	☒
	1.1.1.4 Kleinvolume vloeistoffen - Radiofarmaceutica	☒	☐
	1.1.1.5 Vaste toedieningsvormen en implantaten	☐	☒
	1.1.1.6 Andere aseptisch vervaardigde producten, namelijk	☐	☒
	1.1.2 Terminale sterilisatie (van de volgende toedieningsvormen)	☒	☐
	1.1.2.1 Grootvolume vloeistoffen	☐	☒
	1.1.2.2 Halfvaste toedieningsvormen	☐	☒
	1.1.2.3 Kleinvolume vloeistoffen - Radiofarmaceutica	☒	☐
	1.1.2.4 Vaste toedieningsvormen en implantaten	☐	☒
	1.1.2.5 Andere terminaal gesteriliseerde producten, namelijk	☐	☒
	1.1.3 Vrijgifte	☒	☐
1.2	**NIET-STERIELE PRODUCTEN VOOR ONDERZOEK**	☐	☒
	1.2.1 Niet-steriele producten (bewerkingshandelingen ten aanzien van de volgende toedieningsvormen)	☐	☒
	1.2.1.1 Harde capsules	☐	☒
	1.2.1.2 Zachte capsules	☐	☒
	1.2.1.3 Kauwgom	☐	☒
	1.2.1.4 Geïmpregneerde matrices	☐	☒
	1.2.1.5 Vloeistoffen voor uitwendig gebruik	☐	☒
	1.2.1.6 Vloeistoffen voor inwendig gebruik	☐	☒
	1.2.1.7 Medische gassen	☐	☒
	1.2.1.8 Andere vaste toedieningsvormen	☐	☒
	1.2.1.9 Onder druk staande toedieningsvormen	☐	☒
	1.2.1.10 Radionucleïde generatoren	☐	☒
	1.2.1.11 Halfvaste toedieningsvormen	☐	☒
	1.2.1.12 Zetpillen	☐	☒
	1.2.1.13 Tabletten	☐	☒
	1.2.1.14 Transdermale pleisters	☐	☒
	1.2.1.15 Intraruminaal hulpmiddel	☐	☒
	1.2.1.16 Premixen voor diergeneeskundig gebruik	☐	☒

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	1.2.1.17 Andere niet-steriele geneesmiddelen, namelijk	☐	☒
	1.2.2 Vrijgifte	☐	☒
1.3	BIOLOGISCHE GENEESMIDDELEN VOOR ONDERZOEK	☐	☒
	1.3.1 Biologische geneesmiddelen (lijst van productcategorieën)	☐	☒
	1.3.1.1 Bloedproducten	☐	☒
	1.3.1.2 Immunologische producten	☐	☒
	1.3.1.3 Celtherapieproducten	☐	☒
	1.3.1.4 Gentherapieproducten	☐	☒
	1.3.1.5 Biotechnologieproducten	☐	☒
	1.3.1.6 Producten geëxtraheerd uit humaan of dierlijk weefsel	☐	☒
	1.3.1.7 Weefselmanipulatieproducten	☐	☒
	1.3.1.8 Andere biologische geneesmiddelen, namelijk	☐	☒
	1.3.2 Vrijgifte (lijst van productcategorieën)	☐	☒
	1.3.2.1 Bloedproducten	☐	☒
	1.3.2.2 Immunologische producten	☐	☒
	1.3.2.3 Celtherapieproducten	☐	☒
	1.3.2.4 Gentherapieproducten	☐	☒
	1.3.2.5 Biotechnologieproducten	☐	☒
	1.3.2.6 Producten geëxtraheerd uit humaan of dierlijk weefsel	☐	☒
	1.3.2.7 Weefselmanipulatieproducten	☐	☒
	1.3.2.8 Andere biologische geneesmiddelen, namelijk	☐	☒
1.4	ANDERE PRODUCTEN VOOR ONDERZOEK OF BEREIDINGSACTIVITEIT	☐	☒
	1.4.1 Bereiding van:	☐	☒
	1.4.1.1 Kruidenproducten	☐	☒
	1.4.1.2 Homeopathische producten	☐	☒
	1.4.1.3 Overige	☐	☒
	1.4.2 Sterilisatie van werkzame stoffen/tussenproducten/kant-en-klare producten	☐	☒
	1.4.2.1 Filtratie	☐	☒
	1.4.2.2 Droge hitte	☐	☒
	1.4.2.3 Stoom	☐	☒
	1.4.2.4 Chemisch	☐	☒
	1.4.2.5 Gammastraling	☐	☒
	1.4.2.6 Elektronenbestraling	☐	☒
	1.4.3 Overige	☐	☒
1.5	VERPAKKEN VAN GENEESMIDDELEN VOOR ONDERZOEK	☒	☐
	1.5.1 Primair verpakken	☐	☒
	1.5.1.1 Harde capsules	☐	☒
	1.5.1.2 Zachte capsules	☐	☒
	1.5.1.3 Kauwgom	☐	☒

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	1.5.1.4 Geïmpregneerde matrices	☐	☒
	1.5.1.5 Vloeistoffen voor uitwendig gebruik	☐	☒
	1.5.1.6 Vloeistoffen voor inwendig gebruik	☐	☒
	1.5.1.7 Medische gassen	☐	☒
	1.5.1.8 Andere vaste toedieningsvormen	☐	☒
	1.5.1.9 Onder druk staande toedieningsvormen	☐	☒
	1.5.1.10 Radionucleïde generatoren	☐	☒
	1.5.1.11 Halfvaste toedieningsvormen	☐	☒
	1.5.1.12 Zetpillen	☐	☒
	1.5.1.13 Tabletten	☐	☒
	1.5.1.14 Transdermale pleisters	☐	☒
	1.5.1.15 Intraruminaal hulpmiddel	☐	☒
	1.5.1.16 Premixen voor diergeneeskundig gebruik	☐	☒
	1.5.1.17 Andere niet-steriele geneesmiddelen, namelijk	☐	☒
	1.5.2 Secundair verpakken	☒	☐
1.6	**TESTS TEN BEHOEVE VAN KWALITEITSCONTROLE VOOR GENEESMIDDELEN VOOR ONDERZOEK**	☒	☐
	1.6.1 Microbiologisch: steriliteitscontrole	☐	☒
	1.6.2 Microbiologisch: anders	☐	☒
	1.6.3 Chemisch/fysisch	☒	☐
	1.6.4 Biologisch	☐	☒

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[redacted]
2016

Beperkingen of verduidelijkende opmerkingen ten aanzien van de omvang van deze bereidingshandelingen
microbiologie en steriliteitstest worden uitbesteed

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BIJLAGE 2 DEEL 2 - INVOERHANDELINGEN MET GENEESMIDDELEN VOOR ONDERZOEK

		Ja	Nee
2.1	TESTS TEN BEHOEVE VAN KWALITEITSCONTROLE VAN INGEVOERDE GENEESMIDDELEN VOOR ONDERZOEK	☐	☒
	2.1.1 Microbiologisch: steriliteitscontrole	☐	☒
	2.1.2 Microbiologisch: anders	☐	☒
	2.1.3 Chemisch/fysisch	☐	☒
	2.1.4 Biologisch	☐	☒
2.2	VRIJGIFTE VAN GEÏMPORTEERDE GENEESMIDDELEN VOOR ONDERZOEK	☐	☒
	2.2.1 Steriele producten	☐	☒
	2.2.1.1 Aseptisch bereid	☐	☒
	2.2.1.2 Terminaal gesteriliseerd	☐	☒
	2.2.2 Niet-steriele producten	☐	☒
	2.2.3 Biologische geneesmiddelen	☐	☒
	2.2.3.1 Bloedproducten	☐	☒
	2.2.3.2 Immunologische producten	☐	☒
	2.2.3.3 Celtherapieproducten	☐	☒
	2.2.3.4 Gentherapieproducten	☐	☒
	2.2.3.5 Biotechnologieproducten	☐	☒
	2.2.3.6 Producten geëxtraheerd uit humaan of dierlijk weefse[redacted]	☐	☒
	2.2.3.7 Weefselmanipulatieproducten	☐	☒
	2.2.3.8 Andere biologische geneesmiddelen, namelijk [vrije [redacted] 2016	☐	☒
2.3	OVERIGE INVOERACTIVITEITEN MET GENEESMIDDELEN VOOR ONDERZOEK (ELKE ANDERE RELEVANTE INVOERACTIVITEIT DIE NIET DOOR HET BOVENSTAANDE WORDT BESTREKEN)	☐	☒
	2.3.1 Locatie van de fysieke invoer	☐	☒
	2.3.2 Invoer van tussenproducten die verdere verwerking zullen ondergaan	☐	☒
	2.3.3 Biologische werkzame stof	☐	☒
	2.3.4 Overige, namelijk	☐	☒

Beperkingen of verduidelijkende opmerkingen ten aanzien van de omvang van deze bereidingshandelingen

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BIJLAGE 5: QUALIFIED PERSONS (QP'S)
[redacted]
[redacted]
[redacted]

SUMMARY OF PRODUCT CHARACTERISTICS

Ammonia (^{13}N) RTM, solution for injection

Radboud Translational Medicine

1. NAME OF THE MEDICINAL PRODUCT

Ammonia (^{13}N) RTM, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL contains >500 MBq of Ammonia (^{13}N) at date and time of calibration, as mentioned on the label of the secondary container.
The activity per vial ranges from 5 GBq to 10 GBq at the date and time of calibration, as mentioned on the label of the secondary container.

Nitrogen-13 decays to stable carbon-13 with a half-life of 9.96 minutes by emitting a positronic radiation of maximum energy of 1190 keV, followed by photonic annihilation radiations of 511 keV.

Excipient(s) with known effect:
- < 9 mg/ml of sodium chloride

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is for diagnostic use only.

Ammonia (^{13}N) RTM, solution for 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.

4.2. Posology and method of administration

Posology

Rest Imaging Study
The mean recommended activity for an adult weighing 70 kg is 300 MBq but can vary from 100 - 400 MBq depending on the body mass, the type of camera used, and acquisition mode.
Aseptically withdraw Ammonia (^{13}N) RTM, solution for injection from its container and administer as a bolus through a catheter inserted into a large peripheral vein.

Stress Imaging Study
- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia (^{13}N) RTM, solution for injection to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.

- The mean recommended activity for the stress imaging study for an adult weighing 70 kg is 400 MBq but can vary from 200 - 500 MBq. Aseptically withdraw Ammonia (^{13}N) RTM, solution for injection from its container and administer Ammonia (^{13}N) RTM, solution for injection as a bolus after the administration of the pharmacologic stress-inducing drug.

Pediatric population

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the EANM paediatric task group Dosage Card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the body-mass-dependent coefficients given in the table below.

A[MBq]Administered = Baseline Activity × Coefficient

A minimum activity of 21 MBq is recommended.

Method of administration

The injection of ammonium (^{13}N) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

Precautions to be taken before handling or administration of the medicinal product

For instructions on dilution of the medicinal product before administration, see section 10.

For patient preparation, see section 4.4.

The activity of Ammonia (^{13}N) has to be measured with an activimeter immediately prior to injection.

Image acquisition

Start imaging directly after the injection and acquire images for a total of 10-20 minutes.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6)

4.4. Special warnings and precautions for use

Pregnancy, see section 4.6

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Pediatric population

Pediatric population, see section 4.2.

Patient preparation

In order to obtain images of best quality and to reduce the radiation exposure of the bladder,

patients should be encouraged to drink sufficient amounts and to empty their bladder prior to and after the PET examination.

General warnings
Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organization.
Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Specific warnings
This medicinal product contains less than 23 mg per dose, i.e. essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionizing radiation (if there are any) should be offered to the patient.

Pregnancy
Radionuclide procedures carried out on pregnant women also involve radiation dose to the fetus. Only imperative investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and fetus.

Breastfeeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 2 hours and the expressed feeds discarded.

Fertility
No studies on fertility have been performed.

4.7. Effects on ability to drive and use machines
Not relevant.

4.8. Undesirable effects

No adverse reactions have been reported for Ammonia (^{13}N) solution for 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.

Exposure to ionizing radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 1.35 mSv when the maximal recommended activity of 500 MBq is administered, these adverse events are expected to occur with a low probability.

4.9. Overdose

An overdose in the pharmacological sense is unlikely with the doses used for diagnostic purposes.

In the event of administration of a radiation overdose with Ammonia (^{13}N), the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced dieresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, cardiovascular system, other cardiovascular system diagnostic radiopharmaceuticals, ATC code: not yet assigned.

At the chemical concentrations used for diagnostic examinations, Ammonia (^{13}N) does not appear to have any pharmacodynamic activity.

5.2. Pharmacokinetic properties

Following intravenous injection, Ammonia (^{13}N) RTM, solution for injection is cleared from the blood with a biologic half-life of about 2.84 minutes (effective half-life of about 2.21 minutes).
The mass dose of Ammonia (^{13}N) RTM, solution for 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.
Plasma protein binding of Ammonia (^{13}N) or its ^{13}N metabolites has not been studied.

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

<u>Half-Life</u>
In the myocardium, its biologic half-life has been estimated to be less than 2 minutes (effective half-life less than 1.67 minutes).

<u>Renal/Hepatic impairment</u>
The pharmacokinetics in patients with renal or hepatic impairment has not been characterized.

Paediatric population
The pharmacokinetics of Ammonia (^{13}N) RTM, solution for injection have not been studied in pediatric patients.

5.3. Preclinical safety data
Long term animal studies have not been performed to evaluate the carcinogenic potential of Ammonia (^{13}N) RTM, solution for injection. Genotoxicity assays and impairment of male and female fertility studies with Ammonia (^{13}N) RTM, solution for injection have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sodium chloride
Water for injections

6.2. Incompatibilities
This medicinal product must not be mixed with other medicinal products.

6.3. Shelf life
The shelf life of Ammonia (^{13}N) RTM, solution for injection is 40 minutes from End of Synthesis.

6.4. Special precautions for storage
Store below 25 °C in a radiation-shielding container. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5. Nature and contents of container
Pack size: One multidose vial contains 9 to 10 mL of solution, corresponding to 5 to 10 GBq at calibration time.

6.6. Special precautions for disposal and other handling

General warning:
Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organization.
Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

The administration of radiopharmaceuticals creates risks for other persons due to external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must be taken.

If the integrity of the vial is compromised, it should not be used. Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Radboud Translational Medicine B.V.
Geert Grooteplein 21, hp. 142
6525 EZ Nijmegen, the Netherlands
Tel. +31(0)24-3613136
Email: info@ radboudtranslationalmedicine.nl

8. DATE OF REVISION OF THE TEXT

20-06-2017

9. DOSIMETRY

The below table shows the dosimetry as calculated according to the ICRP (International Commission on Radiological Protection) publication 53.

Organ	ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (mGy/MBq)				
	Adults	**15 year old**	**10 year old**	**5 year old**	**1 year old**
Adrenals	2.3E-03	2.6E-03	4.2E-03	6.7E-03	1.3E-02
Bladder wall	8.1E-03	9.9E-03	1.5E-02	2.4E-02	4.5E-02
Bone surfaces	1.6E-03	1.9E-03	3.1E-03	5.1E-03	9.9E-03
Brain	4.2E-03	4.4E-03	4.7E-03	5.2E-03	7.3E-03
Breast	1.8E-03	1.8E-03	2.8E-03	4.6E-03	8.9E-03
GI-tract					
Stomach wall	1.7E-03	2.1E-03	3.2E-03	5.2E-03	9.9E-03
Small intest	1.8E-03	2.2E-03	3.5E-03	5.6E-03	1.1E-02
ULI wall	1.8E-03	2.1E-03	3.4E-03	5.6E-03	1.0E-02
LLI wall	1.9E-03	2.1E-03	3.4E-03	5.4E-03	1.0E-02
Heart	2.1E-03	2.6E-03	4.0E-03	6.1E-03	1.1E-02
Kidneys	4.6E-03	5.7E-03	8.5E-03	1.3E-02	2.4E-02
Liver	4.0E-03	4.9E-03	7.8E-03	1.2E-02	2.3E-02
Lungs	2.51-03	3.0E-03	4.8E-03	7.9E-03	1.5E-02
Ovaries	1.7E-03	2.3E-03	3.6E-03	5.7E-03	1.1E-02
Pancreas	1.9E-03	2.3E-03	3.7E-03	5.8E-03	1.1E-02
Red marrow	1.7E-03	2.1E-03	3.3E-03	5.5E-03	1.0E-02
Spleen	2.5E-03	3.0E-03	5.0E-03	8.0E-03	1.5E-02
Testes	1.8E-03	1.9E-03	3.1E-03	4.9E-03	9.5E-03
Thyroid	1.7E-03	2.2E-03	3.6E-03	5.8E-03	1.1E-02
Uterus	1.9E-03	2.4E-03	3.9E-03	6.1E-03	1.1E-02
Other tissue	1.6E-03	1.9E-03	3.0E-03	4.9E-03	9.4E-03
Effective dose equivalent (mSv/MBq)	**2.7E-03**	**3.2E-03**	**4.9E-03**	**7.7E-03**	**1.5E-02**

The effective dose resulting from the administration of a (maximal recommended) activity of 500 MBq of Ammonia (^{13}N) for an adult weighing 70 kg is about 1.35 mSv.
For an administered activity of 500 MBq the typical radiation doses to the critical organs, liver, brain and bladder are 2.0, 2.1, and 4.1 mGy, respectively.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The pack must be checked before use and the activity measured using an activimeter.

The medicinal product may be diluted with sodium chloride 9 mg/mL solution for injection.

Withdrawals should be performed under aseptic conditions. The vials must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using authorized automated application system.

As with any pharmaceutical product, if the integrity of this vial is compromised, the product should not be administered.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be administered.

Doc. 25.

Van: meldpunt@igz.nl
Aan: meldpunt@igz.nl
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