CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-372/SE1-003

Administrative Documents

NDA 20-372

Myoview™ Kit for the Preparation of Technetium Tc99m Tetrofosmin

U.S. Patent Information

Title:	"Ligands and Cationic Complexes thereof with Technetium-99m"
Patent Number:	US 5,045,302
Status:	Granted, in force
Date of Grant:	September, 3, 1991
Expiry:	April 10, 2007

EXCLUSIVITY SUMMARY FOR NDA # 20-372 SUPPL #SE1-003

Trade Name Myoview Generic Name Tc99m Tetrofosmin for Injection

Applicant Name:: Amersham Health HFD # 160

Approval Date If Known 02/09/96

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) _SE1____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

___No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /_X/ NO / _/

If yes, NDA #_20-372_. Drug Name _MYOVIEW_____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 11/5/01

Signature Date

Title: RPM

/S/ 11/23/01

Signature of Office/ Date

Division Director

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020372
Trade Name: MYOVIEW (TECHNETIUM TC99M TETROFOSMIN)
Generic Name: TECHNETIUM TC-99M TETROFOSMIN
Supplement Number: 003 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AP **Action Date**: 11/16/01
COMIS Indication: TECHNETIUM TC99M TETROFOSMIN SCINTIGRAPHIC IMAGING FOLLOWING SEPARATE ADMINISTRATIONS UNDER EXERCISE AND RESTING CONDITIONS IS USEFUL IN THE DELINEATION OF REGI

Indication #1: Cardiac perfusion imaging in conjuction with pharmaclogic stress.
Label Adequacy: Other - see comments
Formulation Needed: No new formulation is needed
Comments (if any) The sponsor was denied a waiver, but granted a deferral until pharmacologic stress agents are approved.

Lower Range	Upper Range	Status	Date
Adult	Adult	Deferred	12/21/00

Comments: Pharmacolgic stress agents are not approved for use in pediatrics

This page was last ~~edited~~ on 1.1/5/01

Signature /S/ Date 11/5/01

17. APPENDIX 5: Pediatric Waiver Request, Phase 4 Commitments, Financial Disclosure
sNDA #20,372: SEI 003 AZ

16:1 Pediatric Waiver Request:

A Full Waiver of the Pediatric Requirements under 21 CFR 314.55 was requested by the Sponsor during review of the original Supplement SEI 003 for Myoview with pharmacologic stress, based on the low incidence of atherosclerosis in this population. In the Approvable Letter of 21 December 1999, the Sponsor was informed that the request for waiver was denied, on the grounds that perfusion imaging may be as clinically beneficial in children as in adults. The Letter also indicated that the Sponsor may submit a request for deferral of the requirement for a "reasonable time" (e.g. until after approval of a pediatric stress agent). The Sponsor has requested this deferral in the current submission. In a subsequent submission (Correspondence 1, 8/1/00), however, the Sponsor has re-requested a complete waiver of the Requirements. In the opinion of this reviewer, the submitted information does not satisfy these Requirements, but a deferral until approval of a pharmacologic stress agent for use in children is reasonable.

Recommended action: DENIAL OF WAIVER, DEFERRAL OF PEDIATRIC REQUIREMENT

16:2 Phase 4 Commitments:

In the Approvable Letter of 21 December 1999, the Sponsor was also reminded of the Phase 4 commitment to perform pharmacokinetic studies of Myoview in children which was agreed to on 4 February 1996. In the current submission, the Sponsor has replied that the commitment was to be addressed in a separate document late in the summer of 2000. Submitted on 1 August 2000, this correspondence also re-requested a Full Waiver of the Requirements for pediatric studies. (see #16.1 above) The Sponsor has elected *not* to furnish the pharmacokinetic data, justifying that the need to determine a pediatric dose is satisfied by "well established methods of dosing adjustments for the pediatric population". A supportive article from the *Journal of Nuclear Medicine Technology* (Veitch, JNMT 2000; 28:69-75) was submitted with a table of dose adjustments by age, body surface area, body weight, or estimated weight of the organ to be imaged. A total of 5 formulae for pediatric dosing were included.

Though the submitted reference by T. Veitch provides clinically accepted methods for dose calculation in children, it cannot replace actual measurements of organ dose which would be obtained in a PK study. Therefore, in the opinion of this reviewer, the article (and submission) does not satisfy the requirement for a Phase 4 commitment agreed upon on 4 February 1996.

Recommended action: DENIAL OF WAIVER OF PHASE 4 COMMITMENT

16:3 Financial Disclosure Statement:

The Sponsor has declined to provide financial disclosure information for the blinded readers involved in Study Reports 2954A and 2955A on the grounds that, under 21 CFR 54.2 (d), these individuals do not meet the requirements and are thus exempt (page 3, Vol. 1 of submission). Review of the Code of Federal Regulations (21, Parts 1-99, page 286) indicates that financial disclosure is necessary for any investigator or sub-investigator "who is directly involved in the treatment or evaluation of research subjects". In the current submission, the Myoview and Tl-201 scans of research subjects were evaluated by the blinded readers, whose interpretations were provided in support of an efficacy claim. Therefore, in the opinion of this reviewer, financial disclosure information from these investigators should be submitted.

Recommended action: REQUEST FOR FINANCIAL DISCLOSURE INFORMATION

III. Debarment Certification

Medi-Physics, Inc., doing business as Nycomed Amersham Imaging, certifies that no individuals debarred under §305 (a) or (b) of the Food, Drug and Cosmetic Act contributed in any way to this Supplement.

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ON ORIGINAL

Overall Supplemental NDA Summary

Introduction

The original New Drug Application (NDA) for MYOVIEW® (Kit for the Preparation of Technetium Tc99m Tetrofosmin for Injection) was approved by the Agency in 1996 for scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions in the delineation of regions of reversible myocardial ischemia in the presence of or absence of infracted myocardium.

Exercise stress testing has demonstrated good sensitivity and specificity for coronary artery disease (CAD) assessment overall; however, the test is much less useful when subjects have a limited exercise capacity because of non-cardiac factors, and it cannot be used if a subject is completely unable to exercise. The past few years have seen a growth in non-exercise pharmacologic stress testing, and MYOVIEW is frequently used with these agents in the clinic.

Medi-Physics Inc., has conducted studies to establish the safety and efficacy of MYOVIEW when used with pharmacologic stress agents for myocardial perfusion imaging. This supplemental NDA presents the data from the studies along with literature which support the use of MYOVIEW with pharmacologic stress agents. Medi-Physics Inc., proposes to revise the labeling for MYOVIEW to include the indication:

DRAFT

The information included in this Supplement show that the safety profile of MYOVIEW does not change when used with pharmacologic stress agents. The data also show that overall, the frequency ant types of adverse events seen with the three pharmacologic stress agents used in these studies were generally similar to those noted in the package insert and in the literature for the respective agents.

Therefore, an additional benefit, as documented in this Supplement is the safety and efficacy of MYOVIEW when used in conjunction with pharmacologic stress agents in patients unable to exercise.

Background

Myocardial scintigraphy using the radiopharmaceutical Thallous Tl201 Chloride Injection has been an established diagnostic imaging procedure in Nuclear Medicine/Nuclear Cardiology units in medical institutions in this country for a number of years. Data provided by this procedure are complementary to other techniques such as coronary angiography, ultrasound cardiology, exercise/stress ECG and clinical laboratory testing in the management of patients with coronary artery disease. The procedure is essentially non-invasive and is limited only by the radiation dose delivered to patients and their ability to perform exercise or stress testing. Thallous Tl201 Chloride Injection, is however, based upon radioactive ^{201}Tl as its active ingredient and this radionuclide has sub-optimal imaging characteristics and limitations on dose administration.

The imaging characteristics of ^{99m}Tc are universally recognized as being optimized to modern gamma cameras and Single Photon Emission Computed Tomography (SPECT) instruments. The short physical half-life of ^{99m}Tc , 6 hours, permits administration of multi-millicurie doses with acceptable patient radiation dosimetry. The availability of the radionuclide from convenient sterile generator systems, and the formulation of the cold kits a sterile, lyophilized agent for reconstitution with sodium pertechnetate solution at room temperature ensures that the prepared injection is available for both routine and emergency use.

Technetium Tc99m tetrofosmin is a diagnostic radiopharmaceutical . The diagnostic efficacy of an imaging radiopharmaceutical depends upon its selective uptake in the desired target organ or tissue and its exclusion or clearance from adjacent tissue. The greater the difference between these two parameters, the higher the contrast of target versus non-target tissue in the resulting scintigraphic images. In the case of an agent designed to visualize myocardial perfusion defects resulting from infarction and/or reversible myocardial ischemia, the most important characteristics of the agent are:

- a positive correlation between myocardial uptake and blood flow
- a moderate to high myocardial extraction and rapid subsequent clearance of residual blood activity
- retention with minimal redistribution in the myocardial tissue for a period long enough for image acquisition
- minimal uptake and/or rapid clearance from lung and subdiaphragmatic organs
- lack of pharmacologic action and interaction with the wide spectrum of cardioactive therapeutic drugs.

For more than a decade the simple radioactive cationic species $^{201}Tl^{+}$, in Thallous [201Tl] Chloride Injection has been the 'gold standard' for the scintigraphic visualization of myocardial perfusion defects. It satisfies all the above criteria, with the added advantage that it slowly redistributes from well-perfused tissue to reversibly ischemic tissue with a stress-induced reduction in blood flow returns to normal. It does, however, suffer from

some physical and practical disadvantages. Its photon emission spectrum includes only a relatively low proportion of emissions with energies suitable for scintigraphic detection, but a high X-ray contribution which increases the patient radiation dose. This factor, combined with its 73-hour half-life, restricts the permissible administered dose to about 2mCi with resultant sub-optimal count density and then resolution in the scintigraphic images. Also, because ^{201}Tl is cyclotron produced and has a relatively short half-life its availability, especially for emergency use ,is somewhat restricted.

Radiopharmaceuticals labeled with technetium-99m (Tc-99m), on the other hand, offer distinct advantages over thallium-201 from an imaging perspective. Technetium-99m's higher energy of 140 keV results in less attenuation and scatter, with improved image resolution and fewer artifacts than seen with thallium-201. The shorter half-life of technetium-99m (6 hours) means that a much higher dose can be administered to subjects without subjecting them to higher radiation exposure. The higher dose produces images with more counts (better resolution) with a shorter acquisition time than is usually used with thallium-201. In addition to all of the criteria listed above, Technetium Tc-99m tetrofosmin does not have the inconvenience of a heating step during prepration.

There are currently two radiopharmaceuticals available for clinical use in myocardial perfusion imaging that are labeled with technetium-99m: sestamibi and tetrofosmin. Neither agent significantly redistributes following injection, so myocardial images obtained several hours after stress still accurately reflect the stress myocardial perfusion pattern. Further, both of these agents demonstrate the higher count rate and reduction in attenuation and scatter expected with technetium-99m labeled radiopharmaceuticals. Both agents, however, have a lower extraction fraction than Tl-201 (Leppo 1989, Glover 1997), and both agents demonstrate an inability to track an increase in myocardial blood flow above 2 mL/min/g (Glover 1990, Sinusas 1994). Despite these limitations, clinical trials have demonstrated that exercise myocardial perfusion imaging with Tc-99m sestamibi (Package Insert for Cardiolite®) or with Tc-99m tetrofosmin (Zaret 1995) has similar sensitivity and specificity for detection, localization, and assessment of the extent of coronary artery disease (CAD) as is seen with thallium-201. Investigators have proposed that the improved image resolution, with less scatter and attenuation, compensates for the slightly lower extraction fraction and the slightly decreased linear relationship to blood flow increase relative to thallium-201 (Glover 1990 and 1997).

Technetium Tc99m Tetrofosmin Injection, a diagnostic radiopharmaceutical approved by the Agency in February 1999, is prepared by reconstitution of Tetrofosmin with Sodium PertechnetateTc99m Injection. It overcomes the disadvantages of Thallous Tl-201 Chloride. Tc-99m tetrofosmin, in addition to the characteristics noted above, demonstrates a rapid clearance from the blood stream and from extracardiac structures (Sinusas 1994). The rapid clearance of Tc-99m tetrofosmin from the liver is especially useful in myocardial imaging following rest injection since it, like other blood flow tracers, is taken up in proportion to blood flow, and the splanchnic bed receives a much higher percentage of cardiac output at rest than during exercise. Thus, Tc-99m tetrofosmin, like other blood flow agents, shows a much higher splanchnic uptake at rest than during exercise. High liver activity has been

shown to interfere with visual and quantitative assessment of myocardial perfusion. The more rapid clearance of Tc-99m tetrofosmin, therefore, should result in less interference from the liver, and possibly the ability to acquire rest images sooner following tracer administration. Rapid liver clearance would also be an advantage during any imaging procedure where the distribution of cardiac output is similar to that of rest, such as in pharmacologic stress testing.

While exercise stress testing has demonstrated good sensitivity and specificity for coronary artery disease (CAD) assessment overall, the test is much less useful when subjects have a limited exercise capacity because of non-cardiac factors, and it cannot be used if a subject is completely unable to exercise. The past few years have seen a growth in non-exercise pharmacologic stress testing, and several agents (e.g., dipyridamole, adenosine) are currently marketed for that indication, while another (dobutamine) is frequently used.

Intravenous dipyridamole was the first pharmacologic stress agent approved for use with myocardial perfusion imaging. Dipyridamole is a potent coronary artery vasodilator, which acts by increasing the interstitial concentration of endogenous adenosine through inhibition of cellular uptake and deactivation of adenosine (Knabb 1984). It is infused intravenously over 4 minutes, has a peak effect 6 to 9 minutes after the start of injection, and its effects can last for 20 to 40 minutes if not reversed by intravenous aminophylline. Adenosine, an endogenously occurring nucleoside involved in the metabolic regulation of coronary vascular tone (Belardinelli 1989), can also be administered intravenously. Endogenous adenosine has a rapid onset of action (1 to 1.5 minutes to peak coronary flow) and an extremely short half-life (5 to 10 seconds), so its effects disappear within seconds after the injection is discontinued. Both agents dilate coronary arteries and increase coronary blood flow. Stenotic vessels, however, are unable to respond to these vasodilators, and blood flow to these vascular beds does not increase. This variation (or inhomogeneity) in coronary blood flow can be tracked by blood flow tracers (e.g., Tc99m tetrofosmin) and subsequent myocardial perfusion images will depict the blood flow inhomogeneities caused by underlying CAD. The change in myocardial blood flow is similar for the two vasodilators at about four to five times resting flow (Rossen 1991), and both agents have been shown to have similar sensitivity and specificity for CAD assessment compared with exercise myocardial perfusion imaging (Josephson 1982, Gupta 1992). Adenosine has been shown to have a greater vasodilator effect on the systemic circulation than does dipyridamole, and generally adenosine produces a greater incidence of side effects (Mohiuddin 1993, Martin 1992).

In contrast to the coronary vasodilators dipyridamole and adenosine, dobutamine (a catecholamine) increases myocardial work through its inotropic and chronotropic effects, so that myocardial oxygen consumption is increased. The increase in myocardial oxygen consumption can only be met by an increase in myocardial blood flow, and ischemia is produced in the areas supplied by stenotic arteries (Krivokapich 1993), where blood flow increase is not sufficient to meet the increasing oxygen demand. Lower peak coronary flow rates (approximately 3.5 times normal) are seen with dobutamine relative to dipyridamole and adenosine; this lower peak coronary flow rate is similar to that seen with maximal

exercise. Dobutamine, used in combination with Tl-201 and Tc-99m sestamibi imaging for detection of CAD, is a comparable pharmacologic alternative to exercise treadmill testing (Elliot 1991, Herman 1994, Pennell 1991). Although dobutamine is not approved for pharmacologic stress in the United States, the data from one study using dobutamine is presented in this Supplement. The inclusion of the dobutamine data are intended to reflect current clinical practice with these classes of pharmacologic stress agents.

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A. Annotated Package Insert

4 pages redacted from this section of the approval package consisted of draft labeling

B. Intended Use

Technetium Tc99m tetrofosmin is a lyophilized cold kit for use in the preparation of a 99mTc tetrofosmin intravenous injection as a diagnostic radiopharmaceutical indicated for use in scintigraphic imaging of the myocardium following separate administrations under stress (exercise and/or pharmacologic) and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

C. Potential Clinical Benefits

The symptoms of angina pectoris reflect the myocardial ischemia which occurs when the cardiac work and myocardial oxygen demand exceed the ability of the coronary arteries to supply oxygen. Angina is characteristically precipitated by exercise or excitement, relieved by rest or sublingual nitroglycerin and can be reproduced predictably each time the patient exerts himself or herself to the same degree. Patients who succumb almost invariably have extensive coronary atherosclerosis and patchy myocardial fibrosis.

Exercise myocardial scintigraphy is a useful tool in the evaluation of patients with known or suspected ischemic heart disease. It provides unique, non-invasive, functional information which is complementary to ECG data and to the essentially structural information obtained from the more invasive technique of coronary angiography.

Although exercise stress testing has demonstrated good sensitivity and specificity for CAD assessment overall, the test is much less useful when subjects have a limited exercise capacity because of non-cardiac factors, and it cannot be used if a subject is completely unable to exercise. The past few years have seen a growth in non-exercise pharmacologic stress testing and several agents such as dipyridamole and adenosine are currently marketed for that indication. In addition, dobutamine, though not currently approved as a pharmacologic stress testing agent, is frequently used.

Intravenous dipyridamole was the first pharmacologic stress agent approved for use with myocardial perfusion imaging. It is a potent coronary artery vasodilator which acts by increasing the interstitial concentration of endogenous adenosine through inhibition of cellular uptake and deactivation of adenosine (Knabb 1984). Adenosine is an endogenously occurring nucleoside involved in the metabolic regulation of coronary vascular tone that can also be administered intravenously (Belardinelli 1989). Endogenous adenosine has a rapid onset of action and an extremely short half-life, so its effects disappear within seconds after the injection is discontinued. Both agents dilate coronary arteries and increase coronary blood flow. Both agents

dilate coronary arteries and increase coronary blood flow. stenotic blood flow vessels, however, are unable to respond to these vasodilators, and blood flow to these vascular beds does not increase. This variation in coronary blood blow can be tracked by blood flow tracers such ad Tc99m tetrofosmin and subsequent myocardial perfusion images will depict the blood flow inhomogeneities caused by underlying CAD. The change in myocardial blood flow is similar to the two vasodilators at about four to five times resting flow (Rossen 1991), and both agents have been shown to have similar sensitivity and specificity for CAD assessment compared with exercise myocardial perfusion imaging (Hosephson 1982, Gupta 1992). Adenosine has been shown to have a greater vasodilator effect on the systemic circulation than does dipyridamole, and generally adenosine produces a greater incidence of side effects (Modiuddin 1993, Martin 1992).

Dobutamine, in contrast, increases myocardial work through its inotropic and chronotropic effects, so that myocardial oxygen consumption is increased. The increase in myocardial oxygen consumption can only be met by an increase in myocardial blood flow, and ischemia is produced in the area supplied by stenotic arteries (Krivokapick 1993), where blood flow increase is not sufficient to meet the increasing oxygen demand.

Dipyridamole, adenosine and dobutamine, used in combination with Tc-99m tetrofosmin is a comparable pharmacologic alternative to exercise treadmill testing.

Overall, the frequency and types of adverse events seen with the three pharmacologic stress agents used in these studies were generally similar to those noted in the package insert and in the literature for the respective agents. As expected, changes in heart rate and systolic blood pressure were less pronounced with the vasodilator pharmacologic stress agents adenosine and dipyridamole compared with the catecholamine pharmacologic stress agent dobutamine.

D. Clinical Data

Four dipyridamole studies, which present assessments of coronary artery disease through comparisons to coronary angiography results in 191 evaluable subjects, are: Protocol P.53-006 (Study Report 2954) with 58 evaluable subjects having dipyridamole/Tc-99m tetrofosmin imaging; Protocol PR95-302 (Study Report 2955), which is a combined dipyridamole/Tc-99m tetrofosmin and dipyridamole/^{201}Tl study in 26 subjects; a study (Fukuzawa 1996) of dipyridamole/Tc-99m tetrofosmin imaging with combined with low-level exercise stress (bicycle ergometer) in 52 subjects (42 patients and 10 healthy volunteers); and a study (Adachi 1995) of dipyridamole/Tc-99m tetrofosmin imaging in 55 evaluable subjects. These studies showed that Tc-99m tetrofosmin is efficacious for rest/stress myocardial perfusion imaging when used with IV dipyridamole pharmacologic stress testing.
Four adenosine studies present assessments of coronary artery disease through comparisons to coronary angiography results in 136 evaluable subjects. The

Cuocolo 1996 study presents a comparison of adenosine/Tc99m tetrofosmin imaging with exercise stress/Tc-99m tetrofosmin imaging in 41 subjects; the Mahmood 1995 study presents the results of combined rest 201Tl and adenosine/low level exercise stress Tc-99m tetrofosmin imaging in 25 subjects; the Cuocolo 1997 study presents the results of adenosine/Tc-99m tetrofosmin imaging and 2-D echocardiography in 26 subjects; and the Takeishi 1998 study presents the results of adenosine triphosphate/Tc-99m tetrofosmin imaging in 44 evaluable subjects.
Data from one multiple pharmacologic stress agent and exercise stress study are also presented. The study was done to determine the impact of stress (exercise or pharmacologic) on myocardial uptake and defect size as determined by Tc99m tetrofosmin single photon emission computerized tomographic (SPECT) imaging.

Although dobutamine is not approved for pharmacologic stress in the United States, the data from one study using dobutamine is presented in this Supplement. The inclusion of the dobutamine data are intended to reflect current clinical practice with these classes of pharmacologic stress agents. The study assesses the diagnostic accuracy of SPECT imaging with Tc-99m tetrofosmin comparing exercise (treadmill) stress and pharmacologic stress with IV dobutamine in 294 subjects. Comparisons were made to coronary angiography results.

In two of the studies IV dipyridamole pharmacologic stress myocardial perfusion imaging with Tc-99m tetrofosmin was compared to coronary angiography to determine sensitivity, specificity, and positive and negative predictive values for Tc-99m tetrofosmin imaging. Also presented here are two articles published in peer-reviewed journals which present results of Tc-99m tetrofosmin myocardial perfusion imaging with IV dipyridamole stress testing, two articles which present results of Tc-99m tetrofosmin myocardial perfusion imaging with IV adenosine stress testing, one article with Tc-99m tetrofosmin myocardial perfusion imaging with IV adenosine triphosphate stress testing, and one article with Tc-99m tetrofosmin myocardial perfusion imaging with IV dobutamine stress testing. All of these articles used coronary angiography as a reference for determining the sensitivity and specificity of Tc-99m tetrofosmin myocardial perfusion imaging either on a per subject or per vessel basis (or both). Significant coronary artery disease was defined as either 50-100% stenosis or 51-100% stenosis in all but one of these studies. In one paper (Adachi 1995), significant coronary artery lesions are described as ≥75% stenosis; but it is not stated whether this value was assessed qualitatively or quantitatively. Since the difference between these two commonly used definitions is minimal (1% stenosis), the results of all studies are combined here, regardless of which definition was used.

A total of 370 subjects underwent pharmacologic stress testing with Tc-99m tetrofosmin and were evaluated by coronary angiography; 190 subjects administered IV dipyridamole, 157 subjects administered IV adenosine (65 of these with adenosine triphosphate), and 23 subjects administered IV dobutamine. For the dipyridamole studies where results were analyzed and available on a per-subject

basis (PR95-302, P.53-006, Fukuzawa 1996), there were 135 subjects with CAD (as determined by coronary angiography) with an overall sensitivity after Tc-99m tetrofosmin imaging of 83% to 100%. Specificity was reported as 31% in P.53-006 and 10 subjects, defined as having low-probability for significant CAD and no CAD by coronary angiography (Fukuzawa 1996), had a normalcy rate of 100%. For adenosine, subject-based results in one study (Cuocolo 1997), where a sensitivity of 88% of 25 subjects was reported. For the 44 subjects reported for adenosine triphosphate (Takeishi 1998), the sensitivity was 89% and the specificity was 86%. For the one article with dobutamine (Thorley 1995), 23 subjects underwent coronary angiography and the sensitivity for detection of CAD per subject was 95% and the specificity was 80%. One additional study not discussed above (Protocol PR96-301) did not include coronary angiography results for the 38 CAD subjects. However, there were 7 subjects enrolled as low-probability (for CAD) subjects who underwent Tc-99m tetrofosmin rest and stress imaging using adenosine, dipyridamole, and dobutamine; exercise stress imaging was used as the reference standard. In this study, 6 subjects had normal images with exercise and dipyridamole (86% normalcy rate for each) and all 7 subjects had normal images with adenosine and dobutamine (100% normalcy rate for both). The low-probability subject with the abnormal Tc-99m tetrofosmin images with dipyridamole was not the same subject as the one with abnormal exercise Tc-99m tetrofosmin images.

The sensitivity was also analyzed in terms of Tc-99m tetrofosmin imaging with pharmacologic stress for detection of CAD in subjects with one-vessel, two-vessel, and three-vessel disease in five studies. For dipyridamole (PR95-302, P.53-006, Fukuzawa 1996), the sensitivity was reported as 75% to 90.5% for one-vessel disease, 83% to 100% for two-vessel disease, and 83% to 100% for three-vessel disease. For adenosine (Takeishi 1998), the sensitivity was reported as 83%, 92%, and 100% for single-vessel, two-vessel, and three-vessel disease, respectively; and as (Cuocolo 1997) 83% and 78% for single and multi-vessel disease, respectively.

Vessel-based results were presented for the individual diseased coronary arteries (LAD, LCx, RCA or PDA). For the dipyridamole studies (PR95-302, P.53-006, Fukuzawa 1996, Adachi 1995) the sensitivity values for Tc-99m tetrofosmin imaging with pharmacologic stress imaging were 35% to 87% for the LAD, 19% to 83% for the LCx, and 75% to 96% for the RCA, respectively. The corresponding specificity values were 44% to 100% (LAD), 79% to 100% (LCx), and 20% and 91% (RCA). For adenosine studies (Cuocolo 1996, Cuocolo 1997, Mahmood 1995), the sensitivity values were 81% to 91% (LAD), 69% to 88% for the LCx, and 73% to 78% (RCA or PDA). The corresponding specificity values were 70% to 100% (LAD), 70% to 86% (LCx), and 70% to 87% (RCA). For the 23 subjects who underwent dobutamine pharmacologic stress testing with Tc-99m tetrofosmin imaging, the sensitivity for detecting angiographically confirmed CAD was 50% for the LAD, 88% for the RCA, and 60% for the LCx. Specificity values were 75% for the LAD, 80% for the RCA, and 88% for the LCx. The Protocol 96-301 study showed no significant difference in stress-induced abnormalities between images

obtained with Tc-99m tetrofosmin imaging during dobutamine stress than those obtained during exercise stress in 31 subjects with known or suspected CAD (no coronary angiography was performed).

This Supplement presents safety data from five clinical studies that evaluated pharmacologic stress with Tc-99m tetrofosmin myocardial perfusion imaging in subjects with known or suspected (CAD). Four studies (PR98-301, PR94-304, PR95-302, and P53-006) involved a total of 438 subjects who each were to receive only one pharmacologic stress agent (i.e., adenosine, dipyridamole, dobutamine). The fifth study (PR96-301) was a comparative trial of Tc-99m tetrofosmin, with each subject undergoing adenosine, dipyridamole, and dobutamine stress, using exercise stress Tc-99m tetrofosmin images as a reference. A total of 49 subjects participated in this study.

Safety data (adverse events, vital signs, and ECGs) were summarized separately by study (and within each study by center) as well as combined across the four studies, when applicable. The fifth study (PR96-301) was a comparative trial of Tc-99m tetrofosmin, with each subject undergoing adenosine, dipyridamole, and dobutamine stress, using exercise stress Tc-99m tetrofosmin images as a reference. A total of 49 subjects participated in this study; safety data were summarized and discussed separately from the single pharmacologic stress studies.

Other relevant information reviewed includes safety data from 1) the published literature, 2) four non-IND, foreign Nycomed Amersham-sponsored studies, 3) spontaneous adverse event reports, 4) an ——— stress/Tc-99m tetrofosmin study (———), and 5) nonclinical data.

In the four single pharmacologic stress agent studies, a total of 724 adverse events were experienced among 319 of the 438 subjects (73%) who received Tc-99m tetrofosmin in these studies. The percentage of subjects who experienced adverse events was generally similar for PR98-301 (85%), PR95-302 (77%), and P53-006 (67%), with a lower percentage found for PR94-301 (25%). The majority (77%) of the adverse events reported occurred in one study (PR98-301); this study was also the largest (N=284) of the four studies. The most frequently reported adverse events were angina pectoris, flushing, and dyspnea, affecting 39%, 36%, and 28% of the subjects, respectively. Only two subjects (both of whom received adenosine stress in PR98-301) had adverse events that were considered related to Tc-99m tetrofosmin, including two episodes of flushing and one episode each of angina pectoris, abdominal pain, and abnormal vision.

A review of adverse events by pharmacologic stress agent was done to ensure that the type and frequency of adverse events reported in these studies were consistent with what is reported in the package insert and literature for the respective stress agents. In two of the four studies (PR98-301 and PR94-304), 317 of 335 subjects (95%) underwent adenosine stress during Tc-99m tetrofosmin myocardial perfusion

imaging. Specific adverse event frequency rates with adenosine in PR98-301 were similar to those noted in the package insert and in the literature for adenosine; the frequency rates in PR94-304 were lower compared with the package insert/literature. In the other two studies (PR95-302 and P53-006), all subjects (90/90), by study design, underwent dipyridamole stress during Tc-99m tetrofosmin myocardial perfusion imaging. Again, the occurrence of adverse events/symptoms seen with dipyridamole in these studies was consistent with that noted in the package insert and in the literature for dipyridamole. Thirteen subjects underwent dobutamine stress in PR98-301 and one subject underwent dobutamine stress in PR94-304. The frequency and type events seen were similar to those noted in the literature for dobutamine.

For the 26 subjects who underwent stress thallium-201 imaging in PR95-302, 17 subjects (65%) experienced at least one adverse event. The frequency and type of adverse events were similar to that seen for subjects in this study who underwent stress Tc-99m tetrofosmin imaging.

In the one multiple pharmacologic stress agent study a total of 170 adverse events were experienced among 44 of the 49 subjects (90%) in PR96-301. The greatest percentage of subjects who experienced adverse events was for those who received adenosine (97%) followed by dobutamine (82%), dipyridamole (69%), and exercise (35%). The most frequently reported adverse events were angina pectoris (47%), flushing (47%), and headache (41%). In each case, these adverse events occurred more often with pharmacologic stress than with exercise. No adverse events were considered related to Tc-99m tetrofosmin.

Statistical analysis of adverse events for the 38 subjects who underwent all four stress studies revealed a statistically significant difference ($p<0.001$) among the stress studies with respect to the occurrence of at least one adverse event. The frequency and type of adverse events seen with each stress agent in this study were similar to those noted in the package insert and in the literature for the respective agents.

No deaths occurred in the five pharmacologic stress studies reported in this Supplement. In the multiple pharmacologic stress study (PR96-301), two subjects were discontinued from the study because of serious adverse events they experienced during the exercise stress test. One subject's adverse events (ventricular tachycardia and dyspnea) resolved without intervention, whereas the other subject's adverse events (marked ST segment changes and angina) resolved after treatment with sublingual nitroglycerin (2 tablets).

There were no other significant adverse events reported in these studies.

E. Animal Studies

Animal studies also support the efficacy of Tc-99m tetrofosmin with pharmacologic stress imaging. Thallium-201, the first myocardial perfusion imaging agent to attain wide-spread clinical use, has a relatively high extraction fraction and its uptake remains linearly related to coronary blood flow at flow rates 2-3 times that of resting flow. Both Tc-99m labeled myocardial perfusion imaging agents, Tc-99m sestamibi, and Tc-99m tetrofosmin are larger molecules and are taken up by passive diffusion rather than active transport like Tl-201. Both have demonstrated lower extraction fraction than Tl-201, and both show an inability to maintain uptake linearly related to myocardial blood flow at flow rates above 2 times resting flow. Two tracers labeled with the same radioisotope cannot be discriminated in the multi-channel analyzers used to measure exact amounts of tracer deposited in myocardial regions in animal studies. Thus, head-to-head comparisons between Tc-99m sestamibi and Tc-99m tetrofosmin have not been done. Studies where comparable animal models have been used to compare each of these tracers to Tl-201 have shown significant differences between the Tc-99m labeled agent and Tl-201. The results found for each of the Tc-99m labeled agents have been similar and much closer than either agent's results have been to Tl-201. The differences seen between Tl-201 and Tc-99m sestamibi have not translated into a difference in Tc-99m sestamibi's clinical efficacy as a myocardial perfusion imaging agent with pharmacologic stress testing. The clinical results for Tc-99m tetrofosmin presented here demonstrate that the differences seen in animal studies between Tl-201 and Tc-99m tetrofosmin are also not clinically relevant to Tc-99m tetrofosmin's efficacy with pharmacologic stress testing.

Table A summarizes the results from comparative nonclinical studies with ^{201}Tl, Tc-99m tetrofosmin, and Tc-99m sestamibi.

Table A

Results From Nonclinical Studies With Animals Imaged After Pharmacologic Stress

	Species	^{201}Tl	Tc-99m tetrofosmin	Tc-99m sestamibi
First-pass extraction fraction	Dog (Glover, 1997)	82-88%	54.0 ±3.7%	68.3 ±4.7%
	Dog (Hellmuth 1997)	88 ±2.1%	-----	-----
	Rabbit (Tallefer 1999)	Emax = 0.73	Emax = 0.37	Emax = 0.39
	Rabbit (Leppo 1989)	Emax = 0.73	-----	Emax = 0.39
LAD to LCx activity ratio Mild stenoses Critical stenoses	Dog (Glover 1997)	0.58 ±0.04 0.37 ±0.04	0.81 ±0.04 0.67 ±0.05	-----
Stenotic (LAD) to normal (LCx) activity ratio Mild stenoses Critical stenoses	Dog (Glover 1995)	0.62 ±0.04 0.37 ±0.05	-----	0.79 ±0.03 0.53 ±0.06
Image Defects (lower count ratios; LAD to LCx count ratio) Mild stenoses Critical stenoses	Dog (Glover 1997)	0.74 ±0.03 0.61 ±0.01	0.83 ±0.02 0.69 ±0.02	-----
Mild stenoses Critical stenoses	Dog (Glover 1995)	-----	-----	0.80 ±0.02 0.62 ±0.05
Correlation of activity and regional myocardial blood flow	Dog (Sinusas 1994)	-----	Plateaus at 2.0 mL/min/g	Plateaus at 2.0 mL/min/g

These nonclinical studies demonstrate the equivalency of Tc-99m tetrofosmin and Tc-99m sestamibi in the determination of extraction fraction at high coronary flow rates, activity ratios with mild and critical stenoses, and the correlation of activity and regional myocardial blood flow.

F. Conclusions

Overall efficacy results in this submission indicate that Tc-99m tetrofosmin myocardial perfusion imaging, when used with pharmacologic stress testing, demonstrates high sensitivity for the assessment of CAD with coronary angiography as the reference standard. In the two studies where it was calculated, the normalcy rate was 86 to 100%. The specificities are lower and specificity values are more variable across the studies presented here, most likely reflecting both pretest selection and post-test referral biases. The high prevalence of CAD across all studies is an indication of pretest selection bias, and the exclusion of subjects who did not undergo cardiac catheterization (post-test referral bias) will eliminate most subjects with completely normal stress tests and perfusion images. This is especially true when cardiac catheterization is performed on clinical grounds and when the noninvasive assessment is as well established as myocardial perfusion imaging. The sensitivity and specificity values demonstrated by these studies are comparable to those seen with other myocardial perfusion imaging agents when used with exercise and pharmacologic stress tests, and are comparable to values found in the package inserts for dipyridamole and adenosine. They are similar to those for Tc-99m tetrofosmin with exercise stress testing (Zaret 1995, MYOVIEW® package insert). The results for Tc-99m tetrofosmin imaging were comparable to those of Tl-201 when the two agents were compared in the same subjects administered dipyridamole as the pharmacologic stress agent (Protocol PR95-302).

In general, sensitivity for detecting coronary artery disease increased in these studies with the number of diseased vessels present. The highest sensitivity was seen in subjects with three-vessel disease (documented by coronary angiography), and the lowest for those subjects with one-vessel disease. These findings are consistent with those seen with other myocardial perfusion imaging agents, and are because of the increased likelihood of detecting abnormalities that involve a greater amount of the myocardium.

The results for sensitivity and specificity at the per-vessel level are more variable across all studies for several reasons. First, the correlation between image results and coronary angiography for specific vessels is most accurate in subjects with single-vessel disease and least accurate in subjects with three-vessel disease, because of the relative, not absolute, nature of myocardial perfusion imaging with gamma emitters. Thus, studies with proportionally more subjects with one- or two-vessel disease will show higher sensitivity and specificity than those studies where proportionally more subjects had multi-vessel disease. Second, while there is overall consensus on which regions on myocardial perfusion SPECT images should be assigned to each of the three main coronary arteries, there is some variation in the specific segment assignment. There is also variation from study-to-study in the number of segments that images are divided into for analysis. Assigning more regions to one vessel will increase the sensitivity, and most likely decrease the specificity, for that vessel. A third, related reason is that the studies varied in how

apical segments were assigned to the vascular distribution of an adjacent abnormal segment; in some they were assigned to one specific vessel, and in one they were assigned to two vessels. An arbitrary assignment of apical defects to one or more vessels will increase the sensitivity and decrease the specificity for that vessel (or vessels). In general, however, the lowest sensitivity was seen for the LCx, a finding consistent with other published studies. Also, results are more varied among studies than among pharmacologic stress agents, indicating that there is no consistent difference for Tc-99m tetrofosmin with any pharmacologic stress agent.

Data from animal studies on tracer uptake also provide evidence to support Tc-99m tetrofosmin's use as a myocardial perfusion imaging agent with pharmacologic stress testing.

While Tc-99m sestamibi and Tc-99m tetrofosmin show significant differences in extraction fraction compared to Tl-201, the results seen for Tc-99m labeled agents are similar when the same animal model is used. Both agents demonstrate that uptake ceases to be linearly related to myocardial blood flow at a lower flow rate than found with Tl-201, but the results obtained for the two Tc-99m labeled agents are the same. The differences seen in animal studies between Tc-99m sestamibi and Tl-201 have not translated into differences in clinical efficacy between these two agents. Clinical data in the original NDA for Tc-99m tetrofosmin, as well as data presented here, demonstrate the same is true for Tc-99m tetrofosmin.

In summary, Tc-99m tetrofosmin is efficacious at the currently approved dose as a myocardial perfusion imaging agent whose uptake in the myocardium is related to myocardial blood flow and myocardial viability. It allows imaging of myocardial perfusion, and enables detection of perfusion abnormalities, regardless of the mechanism (exercise or pharmacologic stress) which is used to provoke those perfusion abnormalities.

Intravenous administration of Tc-99m tetrofosmin under pharmacologic stress and resting conditions to subjects undergoing myocardial perfusion imaging was found to be safe and well tolerated at doses routinely used for clinical myocardial perfusion imaging. There were no serious adverse events associated with MYOVIEW® nor were there significant trends or individual changes in any safety parameter.

Overall, the frequency and type of adverse events seen with the three pharmacologic stress agents (adenosine, dipyridamole, and dobutamine) used in these studies were generally similar to those noted in the package insert and in the literature for the respective agents. As expected, changes in heart rate and systolic blood pressure were less pronounced with the vasodilator pharmacologic stress agents adenosine and dipyridamole compared with the catecholamine pharmacologic stress agent dobutamine.

G. Foreign Marketing History

MYOVIEW® is marketed in 27 countries around the world at the time of filing of this Supplement.

H. Chemistry, Manufacturing and Controls

There are no changes to the chemistry, manufacturing and controls of the drug product due to this Supplement.

I. Discussion of the Benefit/Risk Relationship

A discussion of the risks and benefits of Technetium Tc-99m tetrofosmin must take in to account that it is a diagnostic radiopharmaceutical administered at extremely low levels of less than 0.23 mg/injection. Patients will usually receive two doses, one at stress and one at rest.

The risks from administration of Technetium Tc-99m tetrofosmin are minimal. As reported in the original NDA, preclinical studies in the rat, guinea pig and mini pig showed good heart uptake with rapid clearance from liver, lung and blood. Acute intravenous toxicity studies in rats and rabbits showed no mortalities at doses up to 1500 times the proposed maximum single human dose. No mortalities at daily doses of up to 1000 times the maximum single human dose were seen in subacute, 14 days, multiple dose studies in rats and rabbits. Pharmacological studies in rats showed only bradycardia at doses of 1050 times the maximum single human dose.

Patient exposure to Technetium Tc-99m tetrofosmin in routine clinical use has been calculated for the period of November 1, 1997 to July 31, 1998, to be more than ——— administrations . ——— ıtients. No new safety issues have been identified during the period of routine clinical use since approval of the product in Denmark in 1993.

The radiation dose to the patient resulting from administration of the agent should always be considered in relation to its diagnostic value. This is particularly relevant to subjects under 18 years of age and to women of child bearing potential. The radiation doses for the 99mTc are broadly comparable to those from other radiopharmaceuticals and from X-ray procedures.

As with all other radiopharmaceuticals, administration is not recommended during pregnancy except where medical opinion deems it necessary. In nursing mothers, it is wise to discontinue breast-feeding after administration of MYOVIEW® as no data are available on the appearance of radioactivity in the milk. Additionally, no other data are available on the use of the product in children. Although no drug

interactions have been identified to date, potential users should be reminded that pharmacologic stress agents may cause adverse reactions.

The use of Technetium Tc-99m tetrofosmin in myocardial perfusion imaging for the assessment of coronary artery disease is well known. An additional benefit, as documented in this Supplement is the safety and efficacy of the product when used in conjunction with pharmacologic stress agents in patients unable to exercise.

References

Please note that the references sited within this summary can be found in their entirety in the Bibliography section of this report located in Volume 9.

4. Technical Information

There are no changes to the chemistry, manufacturing and controls of Myoview® as a result of this Supplement. This section is not applicable. All current CMC information may be found in t he original NDA and Supplements S-001 and S-002.

Clinical Team Leader Memo

NDA:	20372- SEI 003 AZ (Efficacy Supplement; date June 27, 2000)
Sponsor:	Nycomed Amersham, Inc
Drug:	MYOVIEW (Tc-99m tetrofosmin)
Category:	Diagnostic Radiopharmaceutical
Route/dose:	Intravenous; 5 to 8 mCi - stress and 15 to 24 mCi - rest
Modality:	Single Photon Emission Tomography (SPECT)
Related Drugs:	Thallium (T1 201), Cardiolite (Tc99m sestamibi)
FDA Review Team:	MO: Arnstein, M.D; Statistician: Mucci, Ph.D; CSO: Ms. Stewart

Related Reviews and References:

Clinical:	Nelson Arnstein, M.D (November 2000)
	MO review (exercise stress NDA, June 1993)
Statistics:	Tony Mucci, Ph.D. (November 2000, February 1999)
Memo:	Clinical Team Leader & Divisional Director (December 1999)
Action Letter:	December 1999
Meeting Minutes:	February 2000

BACKGROUND

Myoview was approved in 1996 with the following labeling for exercise stress imaging-

"Myoview is indicated for scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium."

An efficacy supplement was submitted on February 27, 1999 for expansion of the existing exercise indication to include pharmacological stress-

DRAFT

This supplement included reports from 5 sponsor conducted clinical trials (of which P53-006 and PR95-302 were identified as pivotal) and seven peer-reviewed articles (of which one was identified as potentially supportive) from the medical

literature. On December 21 1999, an Approvable Action letter was issued which identified several flaws and deficiencies related to the sample size (total N=83 for the two pivotal trials), consensus reads (lack of independent blinded reads, readers being familiar with the protocol and readers engaged in image acquisition) and the lack of robustness of the data (despite an enriched population). The letter recommended an independent blinded re-read for the two pivotal sponsor conducted trials and a new adequate and well-controlled clinical trial.

In February of 2000 (see meeting minutes), the sponsor proposed a change in the label for use of Myoview in a limited population of patients (patients with known or suspected CAD) and additionally submitted a draft protocol for a new study. The focus of the discussion was whether the results of the blinded re-read on the existing data singularly might be sufficient and supportive for such a restricted claim. *It was explained to the sponsor that the results of the blinded re-read would have to be more robust than the previous consensus results both on a subject and vessel level and further decisions on the adequacy of the data would be deferred pending the outcome of the results of the blinded re-read.* There were also comments made on the new proposed protocol.

Subsequently (27 June 2000) in support of this restricted claim, the sponsor filed the current supplement with data from the blinded re-reads (from the two previously identified pivotal trials P53-006 and PR95-302) and referenced literature articles and is seeking the following limited indication-

"Myoview is indicated in the scintigraphic imaging of the myocardium following separate administrations under exercise and/or resting conditions.

DRAFT

It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

DRAFT

EFFICACY FOR THE RESTRICTED CLAIM

Brief description of the two pivotal studies:

The efficacy data stems from two studies that used Dipyridamole as the pharmacologic stress agent and angiography furnished the Standard of Truth for both studies. The larger of the studies (P53-006, total N = 49 for the blinded re-read and 58 for the earlier consensus read) was open-labeled to evaluate Myoview perfusion images with the use of dipyridamole in the assessment of coronary artery disease. The smaller of these trials (PR95-302, total N = 19 for the blinded re-read and 25 for the earlier consensus read) compared dypridamole-Thallium with dypridamole-Myoview SPECT images in patients with coronary artery disease. Both studies were initially read as "consensus" blinded reads and the re-reads (data in current submission) were performed by three independent blinded readers (separate readers for each study). The total evaluable patients for the earlier consensus read were 83 and 68 for the current blinded

re-read. The sponsor's reason for this difference is that not all of the original images were "recoverable" for the blinded re-reads (see Dr. Mucci's review comments in the re-read description section).

GENERAL COMMENTS

The Gold Standard, the Indication and the Adequacy of the Database:

A significant limitation resides in the study design for both these trials, in that, the referenced standard of truth (coronary angiography) in itself does not characterize the disease type, (i.e., distinguish ischemia from infarction bearing in mind that the label calls for "delineation of regions of reversible ischemia") other than being supportive of disease detection (on a subject level) or localization (on a vessel level). "Reversibility" is a functional process that calls for disease type distinction (ischemia versus infarct) but lacks an angiographic correlate.

However, historically, clinical trials to identify ischemia have used angiography as a disease standard of truth (CAD) and or an active comparator to evaluate perfusion in the distribution of the diseased vessel. Specifically, *the approval of Thallium as a pharmacological stress perfusion agent was based on disease detection/localization (not type) with CAD as the reference* (Dipyridamole label). *Myoview was approved for exercise stress assessments on reversibility, also with respect to CAD and was compared to Thallium.*

The smaller (N= 19) study (PR95-302) in the current submission has compared Myoview with Thallium. Therefore reliance on such comparative data that may address reversibility is potentially feasible with this study but the small sample size may be a limiting factor. The larger study (N= 49) did not compare Myoview with Thallium. Therefore, evaluation with respect to disease detection is potentially possible from the combined sample size of 68 and evaluation with respect to disease type (ischemia and therefore reversibility and the sought indication) only from the smaller sample size of 19. Whether the data from these sample sizes are adequate for either type of indication needs to be explored.

Data Analyses:

All data were analyzed both on a subject/patient level and vessel level in the two pivotal studies. While the subject level data detects disease (i.e., any perfusion defect at rest or stress = presence or absence of CAD in any vessel), the ability to determine whether the region of abnormal perfusion correlates with the corresponding vessel abnormality (vessel level data) is clinically more relevant and meaningful because such information at a vessel level can be used in planning the appropriate treatment for the patient. A further refinement over the vessel level data that could potentially provide relevant information which could bring Myoview closer to the intended use, is agreement data at a segmental level between Myoview and Thallium. Such segmental analysis was

performed for the consensus read but not for the current blinded re-read (see findings below - Myoview versus Thallium).

Both on subject and vessel levels, if one defect in a given vascular territory/region/segment was fixed (implying infarction) and another segment in the same territory/region/segment reversible (whether partial or complete and implying ischemia), the final scoring was considered "ischemic". Such a scoring is perhaps more meaningful and clinically relevant as identification of such reversible ischemic areas would be helpful in delivering appropriate treatment that potentially may abort infarction.

Although neither the subject level nor the vessel level data can be used to establish the currently sought indication , , the data may potentially be useful to assess Myoview for approval for pharm stress on similar grounds of approval as Thallium (pharm stress) and Myoview (exercise stress). This logically would call for appropriate changes in the label (see below).

Sensitivities and specificities were determined on both levels (subject and vessel) in these two pivotal trials. Although specificity is independent of disease prevalence, the reliance on its value from the blinded re-read is expected to be greater (due to lack of bias on the part of the blinded readers) compared to the consensus read. The significance that one can attribute to such specificity (from the blinded re-read) is negated by the small sample size. However, given that the majority of the evaluable patients were those with disease (CAD), the lack of enrollment of patients who may have non-cardiac causes of their symptoms is of clinical concern.

As the enrolled patients largely included those with known disease (angiographically proven) rather than those in whom it was suspected, the label should be appropriately amended to exclude "suspected coronary artery disease". Additionally, the in the label is not relevant as these studies were not designed for such an evaluation.

On a broader perspective it is perhaps outside the scope of this review to comment on the differences that exist between exercise induced and pharmacologically induced stress (and therefore their assessments), intrinsic differences in the mechanism of action between Thallium (redistribution phenomenon) and Myoview, and also on the limitations of the technology itself (i.e. normal perfusion in the presence of CAD - myocardial stunning). These issues may play an important role in patient management (decisions on which test or agent to use).

Barring these issues (and the narrowness of the database), the merit of the data obviously rests in its robustness and therefore the focus of the analyses particularly would rest in the differences between the consensus read and the blinded re-read. Additionally the robustness of the comparative data between Myoview and Thallium could potentially

drive the sought indication. The outcome of this analysis would have a direct impact in this decision making.or potentially pave the path for the need for a new study.

FINDINGS

Literature:

None of the re-submitted literature articles (as noted by the MO and the Statistician) were identified as being supportive for efficacy. This was based on the observations that none qualified and met the criteria and the requirements of the CDER Guidance for the Industry-Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, May 1996. Additionally, these literature studies were evaluated for the use of approved pharmacological stress agents, and with the use of established stress protocols (exercise or pharmacologic stress agents, not the combination). Articles outside these and those that included other diagnostic modalities in assessments (e.g. echocardiography) were discredited.

Blinded Re-read versus Consensus Read:

The data from the blinded re-read on the 68 (N= 83 for the previous consensus read from the same trials) evaluable patients (N= 19 from study PR95-302/report 2955A and N= 49 from study P53-006/report 2954A) forms the base for this sought indication. This data was derived by the FDA Statistician after a re-analyses from the sponsor submitted raw data. It should be noted that despite the numerical differences (subtle and within statistical expectations and perhaps due to the difference in the number of evaluable patients - 83 versus 68) in the values between the Sponsor analyzed blinded re-read data and the FDA Statistician (Dr. Mucci) re-analyzed data, they are comparable as illustrated by Dr. Mucci (sponsor versus reviewer statistics tables in the appendix section of Dr. Mucci's review). Therefore it is reasonable that any inferences that can are drawn are justified based on this comparability.

For purposes of ease of presentation a majority read (same score that at least 2 readers gave) from the three blinded readers was calculated and has been shown in the table below. As discussed by Dr. Mucci, under the hypothesis of no difference in the consensus versus the majority blinded re-read for sensitivity, specificity and accuracy, respectively, the differences in sensitivities and specificities are statistically significant (p values = .005, and <.001 respectively), while the difference in accuracy are not statistically significant (p value = .13). This is illustrated in the table below.

Table[1]: Sensitivity, Specificity & Accuracy: Comparison to Angiogram Original Consensus Read versus Blinded Re-read for Myoview (M) and Thallium (T)						
STUDY PR53-006 (N= 49)						
	SUBJECT LEVEL (N = 49)			VESSEL LEVEL (N = 147)		
Read	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Original Consensus	.97 (M)	.36 (M)	.84 (M)	.69 (M)	.51 (M)	.59 (M)
Majority[2] Blinded Re-read	.74 (M)	.64 (M)	.71 (M)	.50 (M)	.81 (M)	.67 (M)
Prevalence	.78[3]			.46[4]		
STUDY PR95-302 (N= 19)						
	SUBJECT LEVEL (N = 19)			VESSEL LEVEL (N = 57)		
Read	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Original Consensus	.95 (M) .95 (T)	*NA*[5]	*NA*[5]	.48 (M) .52 (T)	.69 (M) .54 (T)	.53 (M) .53 (T)
Majority[2] Blinded Re-read	.74 (M) .84 (T)	*NA*[5]	*NA*[5]	.43 (M) .64 (T)	.85 (M) .69 (T)	.53 (M) .65 (T)
Prevalence	1.00[5]			.77		
1 = Derived from Dr. Mucci's review (principal tables); PPV and NPV not analyzed 2 = Majority read = when 2 of the 3 blinded readers agreed and scored the same 3 = 11 healthy and 38 with disease; 7/11 were read as healthy 4 = 68 with disease and 79 without disease 5 = All patients diseased in this study						

As discussed above, since the vessel level of analyses is perhaps more clinically meaningful, the table below summarizes the vessel level data from the two trials combined with respect to angiography.

Pivotal Studies: Vessel Level Pooled Data* (Comparison to Angiogram)			
Total number of vessels = 204 (147+57) Prevalence = .55 Diseased vessels = 112 Normal vessels = 92			
Read	Sensitivity	Specificity	Accuracy
Original Consensus	.61	.53	.57
Majority Blinded Re-read	.47	.82	.63
* Derived from Dr. Mucci's review (overview table (1))			

Overall, the pooled results from the two trials as tabulated in the two tables above show that when compared to angiogram, the blinded re-read data (sensitivity, specificity and accuracy) is not superior; if any, is at best comparable to the consensus read on both vessel and subject levels.

Myoview versus Thallium

As discussed above in the general comment section on the issues of the limitations of the gold standard and the sought indication on reversibilty, there is

reasonable justification in comparing Myoview with Thallium. Such comparative data between Myoview and Thallium potentially exists in all the relevant trials in which these two agents were used singularly or in combination, i.e.- the pharmacologic stress Thallium NDA (subject level sensitivity); results from the exercise stress Myoview NDA (comparative sensitivities between Myoview and Thallium with respect to Ischemia/Infarct and at a subject level) and the current Myoview pharm stress smaller comparative trial.

This overview comparison of sensitivities (at subject level) of all these trials with respect to the current data provides a broader picture and paves the path for a better understanding of the strengths and weaknesses of the latter with respect to the currently sought indication. A similar overview comparison at a vessel level is not feasible because such vessel level analyses were not carried across these trials, including the exercise Myoview NDA.

Subject Level Sensitivity Comparisons

Reference Study		Sensitivity
Thallium Pharm Stress Approved NDA (N = 1100 subjects)		.85
Myoview Exercise Stress Approved NDA (N = 142 subjects)		
	Myoview	.75
	Thallium	.78
Myoview Pharm Stress (current) Blinded Re-read		
	Myoview (N = 68 combined)	.78
	Thallium (N = 19 combined)	.84

As shown above, comparison between Myoview and Thallium reveals that the results (sensitivity on a subject level) for Myoview are at best comparable to Thallium and not superior to Thallium. These results are comparable to the Myoview exercise stress results and to the Thallium NDA results on a subject level for sensitivity. However, it is important to recognize that the Myoview exercise results were obtained on planar images in an unblinded fashion.

As discussed above, angiography does not categorize disease type (ischemia versus infarction) and any valid and pertinent data that might address "reversibility/ischemia" rests in the agreement data between Thallium and Myoview. This is shown below (derived from table #5.39 of Dr. Arnstein's review; source - sponsor's submission) for the current submission.

Thallium & Myoview Reversibilty Agreement[1]

Reference Study	Agreement (%)
Myoview Pharm Stress (current) Blinded Re-read	
Subject Level (N = 19 patients)	~ 58 (3 reader average)
Vessel Level[2] (N = 57 vessels)	~ 60[2] (3 reader average)
Myoview Pharm Stress Consensus Read	
Subject Level (N = 83 patients)	~ 80
Vessel Level	~ 78

1 = Segmental level analyses was not performed for the blinded re-read submission because segmental observations within a given subject were not independent according to the sponsor (MO review, 5:2:3:6)
2 = The 3 reader average Myoview vs Thallium vessel level agreement from the FDA Statistician re-analyzed data is 54%.

Given the importance of the agreement results with respect to the sought indication, further evaluation and validation of this was carried out by the FDA Statistician (mean agreement levels; table (5)) who analyzed the agreement data to address issues of "inter drug variability". This was categorized as Myoview vs Myoview, Thallium vs Thallium and Myoview vs Thallium and the scores were 71%, 70% and 54% respectively. This indicated that there is a lower level of agreement across modalities than within modalities.

Thallium & Myoview: Ischemia/Infarct

The data that directly addresses ischemia or infarct (disease type) exists only in the Myoview exercise NDA (refer to MO review June 1993 and Statistics review February 1999). Myoview was compared to Thallium with respect to ischemia or infarct for sensitivity and an agreement between the two drugs was additionally evaluated. The mean sensitivities (%) combined (two studies and two readers) were as indicated below (table (a); page 11 of Dr. Mucci's February 1999 review)

	Thallium	Myoview
Ischemia	74.5	65.5
Infarct	73	73

Data on agreement (probably more important and meaningful than the sensitivity data) on ischemia between Myoview and Thallium in this exercise stress Myoview NDA had poor to fair level of agreement as evidenced by Kappa statistics.

The following inferences were drawn based on the discussions with Dr. Mucci on the comparative data from the exercise stress NDA - the sensitivity data between Myoview and Thallium were comparable, however the more reliable and meaningful data on agreement data was not. Additionally, the sought "reversibility" claim/indication was approved based largely on the sensitivity data at a subject level with respect to CAD.

SAFETY UPDATE

As discussed in the Medical Officer's review (Dr. Arnstein), the Myoview safety profile does not appear to have changed (February 1996 to June 2000). Over all there were 263 adverse events reported. Neither the noted deaths (9), nor the serious adverse events (sources = Spontaneously reported, US clinical trials and Foreign clinical trials; events 111 and subjects 61) were attributable directly to Myoview. These events appeared to reflect the underlying patients' disease or other conditions including that of the co-administered pharmacologic stress agents.

SUMMARY

The blinded re-read results from these two small trials have not proven to be more robust than the consensus read. These results at best are comparable. The results stemming from a further narrowed database on reversibility/ischemia assessments do not support the sought indication. The submitted literature does not add any value to this database. Although the approvals of Myoview for exercise stress (for reversibility indication) and Thallium for pharm stress were based largely on disease detection, the results from an adequate sample size formed the basis for such an action (that additionally evaluated ischemia). Such justification is not currently feasible due to the small sample size. Although these results are at best statistically comparable with respect to coronary artery disease detection, the value and the clinical benefit that this data can render is questionable due to the lack of demonstration of clinical usefulness on a vessel level despite the presence of high disease prevalence.

RECOMMENDATION

Continued "Approvable" status for the currently sought "reversibilitiy" indication with the following recommendations (see previous correspondence)- A new adequate and well controlled clinical trial which would enroll the appropriate patient population (with a high degree of clinical suspicion of a perfusion abnormality rather than known disease and in whom ischemia and assessments on reversibility are crucial) and with an appropriate reference of standard of truth with respect to the sought indication (angiography and or comparator and or truth panel and or a patient follow up outcome design).

/S/ 12/21/00

Ramesh Raman, M.D.
Clinical Team Leader

/S/ 12/21/00

Patricia Love, M.D.
Director, HFD 160

In final
I concur
my memo
12/21/00

cc: NDA Archive, HFD-160 Division File, HFD-160/Stewart/Raman

DIVISION DIRECTOR MEMORANDUM TO THE FILE

NDA:	20,372
DRUG:	Myoview (Tc99m Tetrofosmin)
ROUTE:	Intravenous
MODALITY:	Single Photon Emission Tomography (SPECT)
INDICATION:	Pharmacologic Stressed Induced Perfusion Imaging
SPONSOR:	Nycomed Amersham (Medi-Pyysics, Inc.)
SUBMITTED:	February 27, 1999
PDUFA (10 Mo)	December 26, 1999
PDUFA (12 Mo):	February 26, 2000
COMPLETED:	December 20, 1999

RELATED DRUGS: Thallium (Tl 201), Cardiolite (Tc99m sestamibi)

RELATED REVIEWS:

Clinical	Nelson Arnstein, MD, 12/08/99, Sally Loewke, MD, 12/16/99
Statistics	Tony Mucci, PhD, 12/20/99
Project Manager:	Patricia Stewart, BS

BACKGROUND

Myoview (Tc99m Tetrofosmin) Injection was approved in 1996 for "scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium." This efficacy supplement was submitted to expand the existing indication to include pharmacologic stress as a type of allowed myocardial stress and to add the following sentence:

Formal meetings to discuss the protocol designs, current guidance or the pending NDA submission apparently were not held. Other drugs are under development for similar indications.

CHEMISTRY - The drug formulation and dosage is the same as that for the currently approved regimen.

As currently approved Myoview is provided as a kit containing dried component that are mixed on site with technetium that is derived as a Tc99m pertechnetate eluate. This provides 4-8 ml of reconstituted Myoview with ≤ 30 mcg of Tc-99m that contains a maximum of 240 mCi per vial. The per patient dose is 5-8 mCi injected during peak exercise stress and 15-24 mCi for rest imaging. The latter is given 4 hours after exercise imaging is completed. Imaging should begin 15 minutes after injection.

PHARMACOLOGY-TOXICOLOGY – Additional data were not submitted. The dosing regimen and target population are similar.

CLINICAL PHARMACOLOGY – Detailed drug interaction studies for Myoview and the pharmacologic stress agents were not submitted.

CLINICAL/STATISTICAL

A. Efficacy

In support of the expanded indication, on February 27, 1999, Nycomed-Amersham submitted 12 studies (5 that were conducted by the sponsor and 7 that were reported in the literature). The sponsor's studies were completed around the time of the original approval. The literature articles were published between 1995-98. The reviewers assessed these studies on the basis of the CDER Guidance for Industry-Providing clinical Evidence of Effectiveness for Human Drug and Biologic Products, May 1996. Also, considered are established principles of imaging protocols (e.g., the need for blinding to patient history and truth standard, independent readings, clarity and objectivity in the endpoints, statistical methodology). Additionally, the studies were evaluated for the use of approved pharmacologic stress agents, the use of established stress protocols (exercise or pharmacologic stress only, not the combination). Given these criteria, the medical and statistical reviews determined that 4 of the submitted 12 studies (two sponsor conducted studies and two literature articles) had the potential to provide usable data. All 4 studies had angiography as a standard of truth with a >50% occlusion considered positive. All analyzed both the patient and myocardial region of perfusion in correlation with the angiographically identified vessel abnormality. The reviewers conclude that these studies support an approvable recommendation with a independent re-read of the images.

The essence of the reviewer's recommendation rests upon the fact that all 4 studies contain design and results flaws. In considering their reviews, the key flaws are the following:

1. All four studies use consensus blinded reading.

2. The studied population is very enriched and is not fully representative of the intended clinical population. Specifically, perfusion imaging is apt to be performed in two general patient populations: those who are early in the diagnostic evaluation for cardiac disease and who may have non-cardiac causes of their symptoms and 2) those who have known disease and present for further evaluation. The relative importance of false negative and false positive results in these two populations is different. These 4 study populations were very enriched with known disease patients (e.g., a known positive lesion on angiography, a previous MI, previous CABG or PTCA).

3. The two literature articles had an overlap of patients. Specifically, 7 patients in the larger study of 41 patients were included in the smaller study of 26 patients. Therefore, these are not independent studies. The larger is considered in the overall assessment.

4. The sample size of all 4 studies is small (sponsor study #P53-006 had 58 patients; # PR95-302 had 26 patients, Literature Cuocolo 1996 had 41 patients, Cuocolo 1997 had 26 patients).

Therefore, of the 4 articles, the sponsor study P53-006 was the largest study sponsor conducted study, it used the currently recommended dosing, and was conducted in a highly suspect population. This can be considered as a potentially providing substantial evidence. The design problem is the consensus read. Of the two literature studies, the Cuocolo 1996 study of 41 patients is considered supportive because of the consensus read. The two smaller studies are considered to be too small to provide independent To partially overcome the small sample size concern, the statistical review pooled the data from the two sponsor studies. The following paragraphs summarize the statistician's analysis of the two studies and their combination

Both studies were open label, blinded consensus randomized read of the Myoview images produced at rest and after stress with dipyridamole. The standard of truth was angiography with a >50% occlusion. The analysis was conducted at a patient and vessel level. The region of perfusion abnormality was recorded. The angiogram and the Myoview images were obtained within 2 months of each other. Patients were excluded for unstable angina, less than 1 week post MI, congestive heart failure, cardiomyopathy, severe valvular disease, AV block, LBB, uncontrolled arrhythmia. The key differences in the studies are 1)PR-302 enrolled patients with previously identified stenosis on angiography and 2) this study was conducted with rest imaging followed by stress. The package insert calls for stress imaging first. However, clinically this should not affect the randomized image analysis. Based upon Dr. Arnstein's review the overall patient characteristics are shown in the following table.

Table 1 [a] :Selected Demographics of Studies PR93-302 and P53-006

	Study PR95- 302	P53-006	Total
Gender	M=26, F=0	M=41, F=23	M=67, F=23
Age (mean, range)	62 (44 – 75)	57.3 (36 – 82)	nd [b]
Angiogram > 50% lesion	26/26 (100%) [c]	59/64 (92%)	85/90 (94%)
History of MI	n.r [d]	33/64 (32%)	33/64 (32%)
Previous CABG	n.r.	11/60 (18%)	11/60 (18%)
Previous PTCA	n.r.	11/60 (18%)	11/60 (18%)

(a) Derived from Dr. Arnstein's review page 16
(b) N.d = not determined
(c) Enrollment criteria
(d) N.r. = not reported

Based upon the results presented in Dr. Mucci's review page 4, 20, 21, and 24, the following composite table can be derived. It summarizes the patient level and vessel level results from each of the key studies and their combined results. The angiography results are presented horizontally; the Myoview results are presented vertically. The reference letters N and D respectively represent normal and disease findings. The true positive, false positive, true negative and false negative results are listed after the table.

Table 2 [a] : Comparison of Patient and Vessel Level Results of Myoview Images and Angiography for Study PR95-302, PR53-006 and the Combined Analysis

		ANGIOGRAPHY RESULTS											
		PR95-302				PR53-006				Combined			
MYOVIEW		Patient Level		Vessel Level		Patient Level		Vessel Level		Patient Level		Vessel Level	
		N [b]	D [c]	N	D	N	D	N	D	N	D	N	D
	N	0	1	10	31	4	2	46	25	4	3	56	56
	D	0	24	4	29	9	43	46	57	9	67	50	86

(a) Derived from DR Mucci's review pages 4, 20, 21, and 24
(b) N = normal
(c) D = disease

Study PR95-302:

Patient level: *TP = 24/25 (96%)*
FP = na
TN = na
FN =1/24 (4%)

Vessel Level: *TP = 29/60 (48%)*
FP = 4/14 (29%)
TN = 10/14 (71%)
FN = 31/60 (52%)

Study PR35-006

Patient level: *TP = 43/45 (95%)*
FP = 9/13 (69%)
TN = 4/13 (31%)
FN = 2/45 (5%)

Vessel Level: *TP = 57/82 (70%)*
FP = 46/92 (50%)
TN = 46/92 (50%)
FN = 25/82 (30%)

Combined Results:

Patient level: *TP = 67/70 (96%)*
FP = 9/13 (69%)
TN = 4/13 (31%)
FN = 3/70 (3%)

Vessel Level: *TP = 86/146 (61%)*
FP = 56/146 (39%)
TN = 56/106 (53%)
FN = 50/106 (47%)

Based upon these results, the type of analysis (patient level or vessel level) influences the overall interpretation. On a patient level, the number of patients with a false negative is low (3-5%); however, the number of patients with a false positive is high (69%). These results were derived from an enriched population in which the likelihood of finding disease should be high. These results are consistent. However, on a vessel level, depending upon the study, there is approximately 30-50% false positive rate and a 30-50% false negative rate. This suggests that the findings based upon regional deletion in correlation with the angiographic data were weak. Also, the ability to use these data in a screening population would be suspect.

[Dr. Mucci's review performed a segment level correlation of Myoview with thallium in study PR95-302; however, where the results were discordant, the data were not provided in a manner to allow a determination of which drug result best correlated with angiography.]

Dr. Mucci's review notes that the data support a patient level disease detention indication. Also, he notes that the disease "localization use is not as clinically relevant as the detection of arterial disease". While this might be true is some settings, the ability to determine whether the region of abnormal perfusion correlates with the region of identified vascular abnormality is important in determining whether and what type of surgical treatment should be considered. Also, the approved indication is for delineation of "regions of reversible myocardial ischemia", therefore, for the requested indication, the vessel level analysis is relevant.

Vessel level analyses from the two Cuocolo articles are more consistent with patient level analyses. Vessel level analyses from the other sponsor study of patients with known disease on angiography before imaging are discordant.

A. Safety

As discussed in Dr. Arnstein's review, the Myoview safety profile does not appear to be changed. However, increased adverse events in association with the pharmaceutical stress agent are noted and appear to be similar to those reported in their labeling. A safety update was not submitted during the review process and should be provided in the response to the action letter. The office of compliance completed an inspection of the clinical sites and did not identify any findings that would disqualify the studies.

C. Pediatric Studies:

During the review on October 27, 1999 the sponsor submitted a request to waive the requirement to submit pediatric studies for use in pharmacologic stress[1]. Their position is based upon the Agency's listing of atherosclerosis as a condition for which a waiver might be granted, and the low prevalence of atherosclerosis or ischemic heart disease in pediatric patients. These points are summarized in Dr. Arnstein's review of 12/08/99. His review notes that pediatric patients have a variety of cardiac conditions that may lead to a perfusion study to evaluate ischemia (e.g., Takahashi's Arteritis {Kawasaki's Disease}, cardiomyopathy). Therefore, he recommends a deferral of the request. I agree with Dr. Arnstein's recommendation. Additionally, despite the low prevalence of any one disorder that might lead to perfusion imaging, the collective set of disorders is larger. Also, at this time the pharmacologic stress agents and none of the radiopharmaceutical imaging agents are approved for pediatric use. It is conceivable that the use of the imaging technique may change as the pharmaceutical stress agents are approved for pediatric use. Therefore, the requirement of pediatric studies in pharmacologic stress imaging could be deferred until 3 years after the approval of a pharmacologic stress agent in pediatrics. This option should be noted in the action letter.

[1]Also, the sponsor's letter of October 26, 1999 states that they do have a phase IV commitment to conduct a pharmcokinetic study in pediatrics and that the commitment will be addressed in a separate submission.

ASSESSMENT

Typically radionuclide perfusion studies are completed at critical times in a patient management process. They may be conducted to decide whether to conduct a more invasive angiography, to assist in determining whether surgery or angioplasty should be conducted, or to assess the results of other treatment. As such these studies can impact on patient morbidity and mortality.

At best the database might support labeling for use in a limited population of patients who have known disease or are highly suspect for disease. However, before approval the sponsor's studies should be independently read. On the other hand, the vessel level data from the two studies conducted by the sponsor are less convincing. Whether a repeat independent read will produce the same results is not clear. Therefore, before approval a second study of a larger number patients who are more representative of the target population should be conducted. Another approved Tc99 labeled drug should be used a an active control. Angiography (and clinical follow-up if needed) should be used as truth standards. This type of approach is reasonable in this setting because of the existence of the stress exercise indication and because all of the 12 articles appear to have similar results

ACTION: Approvable with confirmation of results by the following:

1. Independent re-read of the sponsor's studies.
2. Conduct of a study in patients who have an early indication for angiography (e.g., positive stress test but without a known history of MI, CABG, PTCA or previously identified angiographic lesions)
3. Subsequent labeling should describe the patient population used to establish the indication.

Additionally, the letter should note the denial of the pediatric waiver request and should recommend a request for deferral.

MEMORANDUM OF TELECON

DATE: May 7, 2001

APPLICATION NUMBER: NDA 20-372, Myoview (kit for the preparation of Technetium Tc99m Tetrofosmin for injection)

BETWEEN:

Name: Daniel G. Mannix, Vice President, Regulatory Affairs
Phone: 609-514-6494
Representing: Nycomed Amersham Imaging

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The sponsor submitted a position paper dated February 16, 2001, that described how myocardial perfusion agents are used in an actual clinical setting of pharmacologic stress testing and supporting arguments of the clinical utility of patient rather than vessel level analysis. The sponsor proposeded that the Agency reconsider the approvable action of December 21, 2000 based on the new information.

The sponsor was informed that after preliminary review of the general correspondence dated February 16, 2001, the Agency is favorably inclined to consider the new information for review.

Patricia A. Stewart
Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: March 30, 2001

APPLICATION NUMBER: NDA 20-372/S-003, Myoview (Kit for the Preparation of Technetium Tc99m Tetrafosmin for Injection)

BETWEEN:

Name: Stefan J. Ochalski, Senior Manager Regulatory Affairs
Phone: 609-514-6843
Representing: Nycomed Amersham Imaging

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The sponsor submitted a meeting request dated March 20, 2001, requesting that the teleconference scheduled for April 4, 2001, be changed to a face- to -face meeting. The sponsor was told that he would be informed after the review team met internally whether there may be need for a face-to-face meeting instead of the teleconference.

The sponsor was informed that the Agency agreed with their position that the patient level analysis was appropriate based on how the product is used in clinical setting. However the Agency did not think the 2 small clinical studies were robust enough to support a change in the indication. The division was going to consult with DDMAC to see if there was a possibility of including the information in the pharmacodynamics section of the labeling. Since we agreed with their position on patient level analysis, we did not believe that a face-to-face meeting was necessary at this time.

/S/

Patricia A. Stewart
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-372

5/21/01

Nycomed/Amersham
Attention: Daniel G. Mannix, Ph.D.
Vice President Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540-6231

Dear Dr. Mannix:

We received your May 9, 2001 correspondence on May 9, 2001 requesting a teleconference to discuss the information provided by the division after reviewing the general correspondence dated February 16, 2001. We considered your request and concluded the teleconference is unnecessary. However, in order to assist you in your drug development program, we are providing the following information in response to questions included in your meeting request.

Nycomed Amersham Question:

1. *We understand from your statement of May 7, 2001 that you will accept for review a formal resubmission of General Correspondence (originally submitted 16 Feb 01) to our supplement based on a patient-level analysis of our existing database. We acknowledge that without a complete review of any resubmission you cannot predict what the final approvability of the supplement might be. Our planned resubmission will include the Request of Reconsideration Document and proposed labeling. Our resubmission would not include additional data relative to the vessel-level analysis requested in your action letter dated 12/21/2000 nor would it include any new analyses not already submitted in an earlier submission. From a "filing" point of view, will this submission be suitable as a Complete Response to your action letter? If not, what is lacking from this planned submission?*

Agency Response:

The submission as proposed above would not be considered a Complete Response to the December 21, 2000, nor to the December 21, 1999, action letters because of the continued need for the study in a clinically relevant population, however, we will accept it for review of a limited indication. The official resubmission should reference supplemental application NDA20-372/SE-003 dated February 26, 1999. We request the inclusion of all information in the General Correspondence dated February 16, 2001. Also, as noted in the December 21, 1999 and December 21, 2000 approvable letters, submit a financial disclosure statement for the blinded readers and safety update. In addition, to assist in the consideration of a limited indication, we

request an update of the ongoing study in the broader clinically relevant population ———

———

Nycomed Amersham Question:

2. *Referring to our teleconference of 4 April 01, the Division stated that while there is no user fee timeline for this resubmission, the Division could take action in less than six months since an "unofficial" internal decision has already been made. Provided that the resubmission will contain no new clinical study information and that all the data has been reviewed by the Division previously, NAI respectfully requests clarification as to whether this would qualify for a shortened review cycle.*

Agency Response:

In the April 4, 2001, teleconference, the division agreed that the patient level as a primary endpoint could be used. However, we indicated our continued concern about the small sample size of the two key studies. Reviews will need to be officially conducted and written in order to come to a final decision on the supplement. Regarding the timelines of the review, although technically a PDUFA time requirement does not exist for NDA supplement resubmissions, we follow the CDER policy in MAPP 6020.4. This sets an internal goal of 6 months. In the April 4, 2001 teleconference, we indicated that because of our familiarity with the material, it is likely that the review could be completed in less than 6 months. However, actual time will be dependent upon the data submitted and the review itself. A more realistic estimate of the review time can be made after the submission is received and the review is in progress

If you have any questions, contact Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

/S/

{See appended electronic signature page}

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: March 21, 2001

APPLICATION NUMBER: NDA 20-372/S-003, Myoview (Kit for the Preparation of Technetium Tc99m Tetrafosmin for Injection)

BETWEEN:

Name: Stefan J. Ochalski, Senior Manager Regulatory Affairs
Phone: 609-514-6843
Representing: Nycomed Amersham Imaging

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The sponsor submitted a meeting request dated March 20, 2001, requesting that the teleconference scheduled for April 4, 2001, be changed to a face- to -face meeting.

The sponsor was informed that the FDA considers a teleconference a formal meeting and it is at the Agency's discretion whether a meeting is granted and the type of meeting.. Also, the review team would be meeting on March 29, 2001, to discuss the position paper submitted February 16, 2001, and if the Agency was in agreement, there may not be anything substantial to discuss. I told the sponsor I would call after our internal meeting and if we decide a face-to-face meeting will be more appropriate we can reschedule it at that time.

Patricia A. Stewart
Regulatory Project Manager

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
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Message:Clinical comments for NDA 20-372/S-003 for submission #053.

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