CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-372/SE1-003

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-372/SE-003

NOV 32 2001

Amersham Health
Attention: Stefan Ochalski
Senior Manager, Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540-6231

Dear Mr. Ochalski:

Please refer to your supplemental new drug application dated February 26, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myoview™ (Kit for the Preparation of Technetium Tc99m Tetrofosmin for Injection).

We acknowledge receipt of your submissions dated February 13 and 16, April 23, May 14 and 23, August 28, October 3 and 30, 2001. Also, we acknowledge the January 31, 2001, meeting and April 4, 2001, teleconference. Your submission of May 23, 2001, constituted a complete response for the limited indication to our December 21, 1999 and 2000, action letters.

The resubmission for this supplemental new drug application proposes for the use of Myoview™ (Kit for the Preparation of Technetium Tc99m Tetrofosmin for Injection) to add a pharmacologic stress indication.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter for the following expanded indication:

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

Myoview™ is also indicated for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress in patients with known or suspected coronary artery disease."

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999).

Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-372/SE-003." Approval of this submission by FDA is not required before the labeling is used.

A labeling supplement should also be submitted to amend the Myoview24™ package insert to include the new information.

We acknowledge receipt of your July 17, 2001, submission requesting a waiver for the postmarketing study commitments in your submission dated February 9, 1996. The waiver request will be responded to under separate cover. Unless the waiver request is granted, the commitments listed below will remain in effect.

1. Perform a human study to define tetrofosmin's pharmacokinetic and metabolic profile.

2. Perform pharmacokinetic studies to determine if dose adjustment is needed in the pediatric population on the basis of age, weight, body size, renal function and liver function.

We also acknowledge completion of the following postmarketing agreements:

1. Information regarding the MYOVIEW ——, correcting the discrepancy in —— and including a concomitant determination of a reference standard each time the IR release test for P53-SSA is performed.
   Commitment Date: February 9, 1996
   Submission Date: September 4, 1996.

2. Reconstitute one MYOVIEW24 kit with sodium Tc99m pertechnetate at the maximum radioactivity level (400mCi/mL) and follow the ITLC over the course of —— expiration dating period.
   Commitment Date: August 4, 2001
   Submission Date: September 28, 2001

If the post marketing waiver is not granted, submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, ~~as~~ of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an

assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We acknowledge your request for a deferral of the pediatric studies in the resubmission dated June 23, 2000, and our December 21, 2000, approvable letter granting the deferral. The deferral was based upon the fact that pharmacologic stress agents are not approved for use in the pediatric population. We remind you that the deferral is accepted until 5 years after the approval of pharmacologic stress agents in pediatric patients.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call 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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

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Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-372/SE-003

DEC 22 2000

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

Dear Dr. Mannix:

Please refer to your supplemental new drug application dated February 26, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myoview (Tc99m Tetrofosmin for Injection).

We acknowledge receipt of your submissions dated March 3, 6 and 22; June 23 and 29; July 11; August 1; October 13, 16 and 25 and December 11, 2000. Your submission of June 23, 2000, constituted a complete response for the limited indication to our action letter of December 21, 1999.

The resubmission for this supplemental new drug application proposes for the use of Myoview (Tc99m Tetrofosmin for Injection) for the following revised indication. The underlined sentences are additions to the currently approved indication.

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

We have completed the review of this application, as amended, and it remains approvable for the expanded indication of Myoview used in conjunction with pharmacologic stress agents. Before this application may be approved, however, it will be necessary for you to address the following:

The proposed revised indication as stated in the application is an expansion of the existing indication to allow the use of pharmacologic stress in patients with known or suspected coronary artery disease.

In the original approvable letter of December 21, 1999, the literature articles were identified as deficient because of design flaws that included the following: 1) the lack of independent blinded reading, 2) the use of small sample sizes, 3) lack of full protocol descriptions, 4) the lack of a full accounting of patients, 5) the use of atypical stress techniques (e.g., the concurrent use of exercise and pharmacologic stress), 6) the duplicate reporting of the same patients in two literature articles by Cuocolo et. al., 7) the lack of a described statistical analysis, 8) the lack of a description of image quality, 9) the lack of a by-segment analysis, and 10) the lack of a commonly accepted stress regimen.

In the current submission the literature are re-analyzed and several articles were identified as providing core support. However, these articles included 5 that were reviewed previously and contain several of the flaws stated above, 3 newly submitted articles used unapproved pharmacologic stress agents, and one duplicative article reported the Nycomed sponsored studies before the blinded re-read. As noted in the submission, none of these articles can "be considered sufficiently robust". Likewise, because of their collective deficiencies, they are supportive only.

The blinded re-read of the two key studies (P53-006 and PR95-302) was submitted in support of a restricted label expansion in patients with known or highly suspected coronary artery disease. In the original letter of December 21, 1999, both these studies were identified as small (58 and 25 subjects, respectively). In the blinded re-read the number of patients available for analysis has decreased to 49 and 19, respectively. Also, as noted in the original letter, the patient level analysis of these studies reveals a high sensitivity; however, the vessel level analysis is less robust than would be expected in a population with a high disease prevalence rate. In the current analysis, depending upon the vessel and blinded reader, the sensitivities range from 29.6% to 76.2%. On average, by reader, the vessel sensitivities range from 37% to 61%. Given the high prevalence of disease in this population, the clinical value of these results in regional perfusion assessments is not clear.

Therefore, collectively, these data continue to be considered preliminary. In order to resolve these deficiencies, we request the completion of your ongoing study in a clinically relevant population. As noted in the previous letter, such a study would include such features as angiographic or clinical outcome standards of truth, independent blinded reading, an adequate sample size to detect differences, if they exist, and a Tc99m-based active control. We will be glad to continue our ongoing discussion on the protocol for this study.

In addition to the above, the agency letter of December 21, 1999, requested the submission of financial disclosure information on the blinded readers of studies PR95-302 and P53-006. We acknowledge your position that the blinded readers do not meet the definition in 21 CFR54.2 (d) that states that a "clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects". We disagree with that interpretation because the blinded readers supplied the patient evaluation that is critical to the efficacy determination. For imaging trials, in effect the blinded readers are subinvestigators or surrogates for the onsite investigator. They not only influence the overall results of the trial, but they provide the most meaningful, relevant efficacy information. Therefore, the financial disclosure forms are needed from these evaluators and should be provided.

We acknowledge your letter dated August 01, 2000, in which you requested a full waiver of the phase IV commitment of February 9, 1996, and of all requirements under 21 CFR 314.55, regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. The request for a full waiver is based upon the availability of dosing information in the public literature. In support of the full pediatric waiver, one literature review article was submitted that describes approaches for adjusting the dose of radioactivity. This article indicates that several formulas are available to calculate the dose. In the provided example for a 2-year-old child, the different formulas produced a dose range from 1.9 to 3.3 mCi.

The goal of the pediatric dose adjustment information is to provide dose adjustment information in the Myoview label. The supportive data should consider both the radionuclide and the ligand. The

provided literature reference is not sufficient to meet the phase IV requirement or the pediatric rule. Therefore, the full waiver is denied and the phase IV commitment continues. We are available to discuss approaches for fulfilling this commitment.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

We acknowledge your request for a deferral of the pediatric studies, noted in the resubmission. The deferral is based upon the fact that pharmacologic stress agents are not approved for use in the pediatric population. This deferral is accepted until 5 years after the approval of pharmacologic stress agents in pediatric patients.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a

study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed for this indication until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

Patricia Y. Love, MD, MBA
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-372

DEC 21 1999

Nycomed Amersham, Inc.
Attention: Joseph A. Pierro, M.D.
Acting Vice President, Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540

Dear Dr. Pierro:

Please refer to your new drug application NDA 20-372 dated February 26, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myoview (Kit for the preparation of Technetium Tc99m Tetrofosmin for Injection). NDA 20-372/SE-003 provides for the expanded indication of Myoview used in conjunction with pharmacologic stress agents.

We acknowledge receipt of your submissions dated June 2, July 13 and 23 (2); September 21, 22 and 23; October 26, 1999.

We have completed the review of this application, as amended, and it is approvable for the expanded indication of Myoview used in conjunction with pharmacologic stress agents. Before this application may be approved, however, it will be necessary for you to address the following:

The proposed indication as stated in the application is an expansion of the existing labeling by the addition of the underlined wording: "Myoview is indicated in the scintigraphic imaging of the myocardium following separate administrations under stress (exercise and pharmacologic) and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

The submitted studies and literature articles have several protocol design flaws that limit their usefulness or confound the analysis that supports the proposed indication. These issues are discussed below.

Two key studies were conducted (P53-006 and PR95-302). In these studies, the population was significantly enriched with patients who had known cardiac disease and are not representative of the spectrum of patients apt to undergo a pharmacologic stress perfusion image. Specifically, study PR95-302 enrolled patients who had pre-existing stenotic lesions on angiography. Study P53-006 enrolled known or suspected disease patients whose demographics were 92% of patients with greater than 50% stenosis on angiography, 32 % with previous myocardial infarction, 18% with previous coronary

artery bypass graft, and 18% of patients with previous percutaneous coronary angioplasty. While the patient level analysis of these studies reveals a high sensitivity, the vessel level analysis is less robust than would be expected in a population with a high disease prevalence rate. The segmental analysis trends in the same direction; however, these results are inconclusive because of the small sample sizes and the enriched population. Additionally, the studies used a consensus blinded image assessment. The lack of an independent blinded read presents a potential for bias.

Across the other studies and literature articles that were submitted, there were one or more design flaws that include the following: 1) the lack of independent blinded reading, 2) the use of small sample sizes, 3) lack of full protocol descriptions, 4) the lack of a full accounting of patients, 5) the use of atypical stress techniques (e.g., the concurrent use of exercise and pharmacologic stress), 6) the duplicate reporting of the same patients in two literature articles by Cuocolo et. al., 7) the lack of a described statistical analysis, 8) the lack of a description of image quality, 9) the lack of a by-segment analysis, 10) the lack of a commonly accepted stress regimen, and/or 11) the lack of an independent blinded read.

Of these deficiencies, the only retrospectively correctable flaw is the method of image reading. The two studies that are otherwise reasonably designed to support the proposed expanded indication are P53-006 and PR95-302. Therefore, in order to resolve these deficiencies, we request a blinded, independent re-read of the images from these two studies. We strongly suggest that the protocol for this re-read be submitted for review and comment before implementation.

Additionally, to resolve these deficiencies, we request the completion of a study in patients who are early candidates for stress perfusion imaging; e.g., patients who do not have known disease but who meet the clinical criteria for evaluation. Such a study would include such features as angiographic or clinical outcome standards of truth, independent blinded reading, exercise and pharmacologic stress comparisons, an adequate sample size to detect differences if they exist, and ideally a Tc99m-based active control. We will be glad to review a draft protocol before implementation. Alternatively, if such studies are available in the literature, they may be submitted.

Although draft labeling is being deferred until the submission and review of your independent blinded read, the labeling should contain a clinical trials section that adequately defines the studied populations in PR95-302 and P53-006. Also, it should describe the population from any new studies that are found to be acceptable. The labeling should report the results of patient-level and vessel-level analyses. The proposed indications may include restrictions as supported by the reanalysis.

We remind you of your phase 4 commitment of February 4, 1996, to conduct a pharmacokinetic evaluation in pediatric patients. Also, we acknowledge your October 26, 1999 letter that indicates your intent to address this commitment in a separate submission. At this time we expect your compliance with this commitment. We remain available to discuss this protocol with you.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We acknowledge your letter dated October 26, 1999, in which you requested a full waiver of the requirements under 21 CFR 314.55, regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. Your request is specific to the pharmacologic stress imaging indication and is based on the low frequency of atherosclerosis in the pediatric population and the infrequent occurrence of radiopharmaceutical imaging in pediatric patients. While we agree that ischemic atherosclerosis is infrequent in this population, as your submission notes, atherosclerosis is not the only reason for perfusion imaging studies. Also, the Myoview indication is not specific to atherosclerosis. Additionally, the pediatric rule does not contain an automatic exclusion for infrequent use. If the drug use is able to provide benefit, then studies may be required. Perfusion imaging should be able to provide the same clinical benefit in pediatrics as it does in adults. Also, the current infrequent use may be related to the lack of an approved pharmacologic stress agent in pediatrics. Therefore, at this point the waiver is denied. You may submit a request for the deferral of the pediatric assessment (e.g., until a reasonable time after the approval of a pharmacologic stress drug in pediatric patients).

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed for this indication until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

Patricia Y. Love, MD, MBA
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research