

COMMENTS TO BE FAXED TO THE SPONSOR Submission #053

11-20-00

The following question pertains to angiography performed on a subset of enrolled subjects within 2 months of study entry:

- 1) Please clarify for us the factors leading to the decision to perform coronary angiography on a subset of enrolled subjects following the study. Is the decision to angio based on Myoview scan results? Is it based on the "Site Evaluation of Subjects" (pre-enrolment stratification)? Is it based on the initial truth panel assessment?

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FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

3 Number of Pages (including cover sheet)

Date: October 3, 2000

To: Helen Hammes

Fax Number: 609-514-6695

Voice Number: 609-514-6817

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: Draft Clinical and Statistical comments for NDA 20-372/S-003

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Cc:

Orig. NDA 20-372

HFD-160/Div files

HFD-160/Stewart

Medical Officer's Comments
NDA 20-372/SE-Q03
October 3, 2000

- 1) Case report forms for all deaths and serious AE's listed in Addendum A to the Integrated Summary of Safety which were a) spontaneously reported, b) in U.S clinical trials, and c) in foreign clinical trials
- 2) Narrative summary paragraphs of each death and serious AE, including ECG, vital signs, time of AE from dosing, dose(s) of Myoview given, stress agent (or exercise), age, sex, concomitant medications, angiographic findings (if present), coronary risk factors, other medical or surgical conditions, final outcome, etc. Autopsy findings should be included in death summaries, if available.
- 3) A table of all deaths and serious adverse events, with the following columns: Subject ID, study number, sex/age, type of AE, intensity (mild, moderate or severe), time after Myoview dosing, causality (disease, procedure, study drug, other medication), action taken, final outcome. The table may be divided into 3 sections: (spontaneously reported, US trials, foreign trials).

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Statistical Reviewer's Comments
NDA 20-372/SE-003
October 3, 2000

In the new blinded reads four complete sets of Myoview Images from PR95-302 (Subjects 12, 16, 19 ,21) were classified as Non-Diagnostic; in several other cases (Subjects 4, 10, 22) at least one reader (but fewer than all readers) classified Thallium or Myoview images as Non-Diagnostic. In only one case (Subject 16) was the Myoview Image from the earlier submission similarly classified (Not Readable.) Please provide (or direct the Reviewer) to the individual details on these classifications (for example, Case Report Forms.) Also, please elaborate on the similarities/differences between the earlier 'not readable' classification and the current 'non-diagnostic' classification.

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Stewart

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Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet)

Date: June 12, 2000

To: Helen Hammes

Fax Number: 609-514-6695

Voice Number: 609-514-6817

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: Draft Statistics comments for proposed protocol _____

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Cc:

Orig. IND []
HFD-160/Div files
HFD-160/Stewart

Statistical Design Comments/Questions for the Sponsor (Nycomed) r.e. IND }
S-049 Protocol — (Document date 3-29-00):

(1): The statistical reviewer would like further clarification regarding the possible diagnostic criteria involved in the initial assessment of the patients which would dictate/suggest that any particular patient undergo angiography. Is there a diagnostic score, for example, such that any patient with at least this score will be directed to angiography, while all patients with smaller scores will not be so directed, or will the decision for angiography follow looser, less formal criteria?

(2): Angiography results, when available (pre or post the initial assessment by the panel) would seem to dominate any diagnosis. Can the Sponsor indicate circumstances in which the reassessment of the probability of disease, post angiography, would require anything more than the angiography results? Would not these results be sufficient in themselves, so that the final disease assessment could dispense with the information collected in the initial assessment?

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5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet)

Date: May 30, 2000

To: Helen Hammes

Fax Number: 609-514-6695

Voice Number: 609-514-6817

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: Draft Clinical comments for NDA 20-372/S-003 new blinded read protocols

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Cc:

Orig. NDA 20-372

HFD-160/Div files

HFD-160/Stewart

To: Nycomed Amersham
Re: NDA 20-372 S-003
New Blinded Read Protocols (Submitted 3-22-00)

Clinical Comments :

- a) Please provide details of the commercial software used to quantitatively analyze the myocardial images and perfusion defects.
- b) Please inform us as to whether the quantitative polar maps are normalized on a segment-by-segment basis to a previously-obtained set of normal images.
- c) Please inform us as to whether the 4 segments in the apical short-axis slice are equal in size (90 degrees each).
- d) Specificity should also be computed on a by-subject and by-vessel level.
- e) Please furnish us with the training materials for the blinded readers, if possible.
- f) It is not clear if the summed or individual reversibility scores for the SPECT images are to be analyzed as an endpoint in the Statistical Plan. Please clarify if this is to be done, and if so, please describe this analysis.
- g) Further comments or deficiencies may become apparent upon corroboration with the Statistical Reviewer, whose review is not available at the time of writing.

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5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet)

Date: May 25, 2000

To: Helen Hammes

Fax Number: 609-514-6695

Voice Number: 609-514-6817

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: Draft Statistical comments for NDA 20-372/S-003 new blinded read protocols

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Cc:

Orig. NDA 20-372
HFD-160/Div files
HFD-160/Stewart

To: Nycomed Amersham
Re: NDA 20-372 S-003
New Blinded Read Protocols (Submitted 3-22-00)

Comments/Questions on Statistical Methods:

(1): The Protocol stipulates that the Rest and Stress images will each be scored, segment by segment, as 0 = normal, 1= mildly reduced, etc. There will also be a segment by segment perfusion defect characterization: reversible, fixed, etc. Are the latter perfusion defects determined automatically from the indicated scores, (e.g., if Rest = 0, and if Stress =2, then defect= reversible) , or will the readers classify perfusion defects independently of these scores (for instance, a reader might score both Rest and Stress =1, but might classify the defect as partially reversible.) This latter possibility seems extremely unlikely, especially since Stress and Rest images are observed side by side. But I haven't located a description of the procedure which might link scores to perfusion defect classifications. My assumption is that the perfusion classification is calculated automatically from the difference in the Rest and Stress scores. Am I correct?

(2): A SAS diskette will be needed for Efficacy analyses. It might be best to hold off on submission of the diskette until the data and analyses have been submitted, since the preferred formatting of the relevant variables which would be most efficient for statistical review purposes could be conditioned by the details of the submission. I expect we will be able to discuss this formatting at the appropriate time.

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MEMORANDUM OF TELECON

DATE: December 29, 1999

APPLICATION NUMBER: NDA 20-372; Myoview (Tc99m tetrofosmin for Injection)

BETWEEN:

Name: Joseph Pierro and Helen Hammes
Phone: 609-514-6815
Representing: Nycomed Amersham

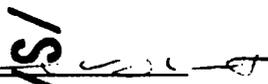
AND

Name: Patricia Stewart
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Discussion/Clarification of correspondence dated December 23, 1999 addressing approvable letter for SE-003 which proposed to add the additional indication for pharmacologic stress.

The letter requested an End of Review Conference under 21 CFR 314.102(d) to discuss the approvable letter dated December 21, 1999. The sponsor was informed that the supplement did not qualify under that regulation because the application was not for a new chemical entity or a major indication. The approval letter clearly stated that the addition of pharmacologic stress was considered an expanded indication not major. The sponsor is entitled to request a "C" or 75 day meeting, but would be required to submit an agenda at least 2 weeks before the meeting. The project manager stated she would set up the meeting and call next week with the date and time.

The letter also requested an extension of the review period of 30 days under 21 CFR 314.110(a)(5). The project manager told the sponsor that the Division Director granted the extension.


Patricia Stewart
Regulatory Project Manager

cc: Original NDA 20-372
HFD-160/Div. File
HFD-160/Patricia Stewart
HFD-160/Mucci

TELECON

MEMORANDUM OF TELECON

DATE: December 15, 1999

APPLICATION NUMBER: NDA 20-372; Myoview (Kit for the preparation of Technetium Tc-99m Tetrofosmin for Injection)

BETWEEN:

Name: Joseph A. Pierro, Judith Murphy, Rocco Ballerini, Mary Ellen Smircich,
Joyce Brobst-Kromer, Helen Hammes
Phone: 610-225-4236
Representing: Nycomed Amersham

AND

Name: Patricia A. Stewart, Patricia Y. Love, A. Eric Jones, Sally Loewke,
Nelson Arnstein, Tony Mucci
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: To discuss with the sponsor the proposed final action for the efficacy supplement SE-003 that proposed to add the expanded indication for pharmacologic stress.

After brief introductions of all participants, the teleconference began with discussion of the current status of the reviews for the application. The sponsor was informed that the Agency had the following concerns with the application:

- Only 4 of the supporting studies that were submitted met the criteria outlined in the guidance document as acceptable and of those, the 2 Cuocolo studies had an overlap of some of the same patients reducing the number of acceptable studies to 3.
- The supporting studies used small numbers and
- All 3 studies employed a consensus read rather than an independent blinded read which is not consistent with the Medical Imaging Guidance Document.
- The patients enrolled in the studies constituted an "enriched population" because they were from an expected diagnosis population or had a known lesion.
- The sensitivity and specificity were different for the subject vs. vessel level. The drug is used as an early evaluation tool so a high sensitivity is desired. Also, the drug is used pre-angiography and/or surgery therefore a high specificity is desired as well.

The Division Director explained that we were leaning toward a non-approval or possibly approvable with a reanalysis of the data from the 2 pivotal trials using an independent blinded read and a new pivotal study enrolling patients earlier in the diagnosis. The current FDA policy is to move toward a complete response, so the NA vs AE action will be addressed at the Office level.

The sponsor explained that the sensitivity and specificity for subject vs. vessel level were different when there was greater disease in certain vessels, but the findings were consistent with Thallium results. With regards to the Agency's concerns about using a "highly enriched

population" the sponsor indicated that in practice, physicians will generally order a cheaper screening method for patients with a low risk of heart disease rather than a SPECT study and a cardiac catheterization. If cardiac catheterization is to be used as the standard of truth, there will be an "enriched population" because catheterization will only be done on patients with a high to moderate risk.

Also discussed was the request for a waiver of the Phase 4 pediatric studies. The Agency indicated that the waiver of the Phase 4 commitments would not be granted but pediatric studies for the pharmacologic stress indication only could be deferred until there was a dosing regimen established for the pharm stress agents.

The Division Director reiterated that we would discuss the issues with the Office before deciding on the final action. We agreed to discuss with the sponsor of the final decision before sending the action letter to allow them the opportunity to withdraw the application.

PSI

Patricia A. Stewart
Regulatory Project Manager

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3 Number of Pages (including cover sheet)

Date: September 17, 1999

To: James Molt

Fax Number: 610-225-4407

Voice Number: 609-514-6403

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: NDA 20,372 Myoveiw Statistical Comments

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Thank you.

cc:

Orig. NDA 20,372
HFD-160/ Div files
HFD-160/ Stewart

Request

The statistical reviewer would like the following data from PR 95-302:

Patient #	LAD (Myo)	LAD (Thallium)	LCX (Myo)	LCX (Thallium)	RCA (Myo)	RCA (Thallium)
1	I, Is, N	I, Is, N				
2						
⋮		etc				
⋮						

26

That is, for each patient, and each vascular area, can the sponsor provide Myonren & Thallium diagnoses:

I = Infarct (Irreversible)

Is = Ischemia (Reversible)

N = Normal

Does this data already exist in the paper submission? (Explicitly)

A fax of such data would suffice.

Question:

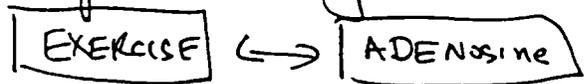
In Cuocolo (97), the following statement occurs:

"In each patient correspondingly resting, exercise and adenosine . . . images were evaluated for direct comparisons."

Does this mean:

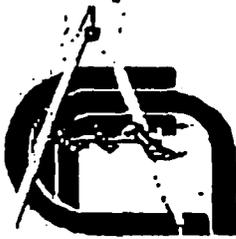
(A) Adenosine Stress Images were examined (together) side-by-side with Exercise Stress Images, and compared 'right on the spot'?

or



(B) Adenosine Stress Images and Exercise Stress Images were examined independently of one another, and then the results were compared?

Stewart



Consiglio Nazionale delle Ricerche
Centro per la Medicina Nucleare
via S. Pansini, 5 - 80131 NAPOLI

FAX MESSAGE

To: Dr. Patricia Stewart
Regulatory Project Manager

Fax: (301) 480-6036

Total No. of pages: 1 (including the present)

From: Alberto Cuocolo, MD

Tel: +39-81-746 2226
Fax: +39-81-545 7081
E-mail: cuocolo@unina.it

Date: September 16, 1999

Dear Dr. Stewart:

About your question, the answer is:

B. Adenosine stress images and exercise stress images were examined independently of one another, and then the results/scores were compared.

I hope that this information will be useful for your work.

Sincerely,


Alberto Cuocolo

cc. NDA 20,372
HFD-160 - Stewart

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
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Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet)

Date: September 15, 1999

To: Alberto Cuocolo, M.D.

Fax Number: 39- 81-545-7081

Voice Number: 39-81-746-3560

From: Patricia Stewart

Regulatory Project Manager

Fax Number: (301) 480-6036

Voice Number: (301) 827-7510

Message: We need clarification how a study was read for an article published in 1996.

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Thank you.

September 14, 1999

Dear Dr. Cuocolo:

I am a Regulatory Project Manager with the Food and Drug Administration in the United States in the Division of Medical Imaging and Radiopharmaceutical Drug Products. I used to work with Vasken Dilsizian in the Department of Nuclear Medicine at NIH and I hope you don't mind that he gave me your fax number. We are currently doing a literature review of stress imaging protocols and would like clarification on how the read was done in the protocol for your article "Technetium 99m-labeled tetrofosmin myocardial tomography in patients with coronary artery disease: Comparison between adenosine and dynamic exercise stress testing" that was published in the Journal of Nuclear Cardiology; May/June 1996. The statistician has the following question that needed clarification:

The following statement occurs on page 3, Data Analysis Section:

"In each patient corresponding resting, exercise, and adenosine Tc99m-labeled tetrofosmin tomographic images were evaluated for direct comparisons."

Does this mean:

A. Adenosine stress images were examined together, side-by-side with exercise stress images, and compared 'right on the spot'?

Or,

B. Adenosine stress images and exercise stress images were examined independently of one another, and then the results/scores were compared?

If you have any problems or questions you can contact me at 301-827-6254 or my e-mail address is stewartp@cderr.fda.gov. Thank you very much for your time.

Sincerely,


Patricia Stewart

MEMORANDUM OF TELECON

DATE: July 6, 1999 (1PM)

APPLICATION NUMBER: NDA 20-372; Myoview

BETWEEN:

Name: Mary Ellen Smircich
Phone: 610-225-4154
Representing: Nycomed Amersham

AND

Name: Toni Mucci
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Statistical Variables for Efficacy Supplement

The statisticians went through the long list of variables that had been faxed to the FDA on June 2, 1999 and determined a smaller more tractable subcollection. The sponsor will fax this shorter list before generating the SAS diskette, so the statistician can perform a preliminary check for accuracy and completeness.

/S/

Toni Mucci

cc: Original 160NDA 20-372
HFD-160/Div. File
HFD-160/Mucci
HFD-160/Stewart ✓

TELECON

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5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet)

Date: June 21, 1999

To: Michael Angioli

Fax Number: 610-225-4407

Voice Number: 610-225-4154

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 443-9281

Voice Number: (301) 827-7510

Message: NDA 20-372 Myoveiw Cinical Comment

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Thank you.

cc:

Orig. NDA 20-372
HFD-160/ Div files
HFD-160/ Stewart ✓

Stewart

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Office of Drug Evaluation III
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Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

3 Number of Pages (including cover sheet)

Date: June 18, 1999

To: Michael Angioli

Fax Number: 610-225-4407

Voice Number: 610-225-4154

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 443-9281

Voice Number: (301) 827-7510

Message: NDA 20-372 Myoveiw Cinical Comments

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cc:

Orig. NDA 20-372
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HFD-160/ Stewart

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DOCUMENT(S) IN DRAFT FORM

MEMORANDUM OF TELECON

DATE: May 27, 1999(2PM)

APPLICATION NUMBER: NDA 20-372; Myoview (Tc99m tetrofosmin for Injection)

BETWEEN:

Name: Michael Angioli, Mary Ellen Smircich, and Dr. Robert Charnigo
Phone: 610-225-4154
Representing: Nycomed Amersham

AND

Name: Patricia Stewart and Toni Mucci
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Discussion/Clarification of Statistical Reviewer's requests that were faxed to the sponsor April 15, 1999.

After brief introductions of all participants, the conference began with the sponsor requesting clarification of the comments that had been faxed. The statistics Reviewer had requested SAS Efficacy diskettes for studies P95-302 and P53-006 and asked for a limited number of variables (less than 100). The sponsor stated that the tables would have more than 100 variables and asked if the reviewer would like 2 tables: 1 with limited variables and 1 with all the variables. The reviewer and sponsor discussed the variables that needed to be included:

Patient ID, age, race, gender
Date of enrollment
Myoview imaging date and dose
Angiogram date and dose
Tl201 imaging date and dose
Diagnoses (scores) by relevant region and by reader for all implicated modalities
(Minimize info to regions used to make diagnosis)
Significant adverse events (2 columns with yes or no)

The reviewer asked the sponsor to send the list of variables with an explanation of each. He said he would review the list and fax comments before the diskettes are sent. The sponsor was in agreement and committed to sending the list of variables.



Patricia Stewart
Regulatory Project Manager

cc: Original NDA 20-372
HFD-160/Div. File
HFD-160/Patricia Stewart
HFD-160/Mucci

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5600 Fishers Lane, Rockville, Maryland 20857

3 Number of Pages (including cover sheet)

Date: April 15, 1999

To: Susan Olinger

Fax Number: 610-225-4407

Voice Number: 610-225-4107

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 443-9281

Voice Number: (301) 827-7510

Message: Statistical comments for sponsor

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HFD-160/Stewart

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DOCUMENT(S) IN DRAFT FORM

MEMORANDUM OF TELECON

DATE: April 4, 2001

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

BETWEEN:

Name: Danniell Mannix, Ph.D., Joseph Pierro, M.D., Robert Carretta, M.D.,
James Kaufman and Stefan J. Ochalski
Phone: 609-514-6843
Representing: Nycomed Amersham Imaging

AND

Name: Patricia Y. Love, M.D., M.B.A., Sally Loewke, M.D.,
Ramesh Raman, M.D., Nelson Arnstein, M.D., Anthony Mucci, Ph.D.
and Patricia A. Stewart
Division of Medical Imaging and Radiopharmaceutical Drug Products,
HFD-160

SUBJECT: At the End of Review meeting, January 31, 2001, the sponsor asked the Agency to reconsider the approvable decision based on the clinical utility of the product and proposed that the patient level analysis was more appropriate than vessel level analysis. The sponsor submitted a position paper and literature review February 16, 2001, outlining how myocardial perfusion agents are used in clinical practice.

The sponsor submitted a meeting request March 20, 2001, requesting that the April 4, 2001, teleconference be changed to a face-to-face meeting and presented the following discussion points:

1. Discussion of the 2/16/01 submission which outlined how agents such as MYOVIEW are actually used in the clinical setting of pharmacologic stress testing and the clinical utility of patient based myocardial perfusion results as opposed to vessel based results.
2. Reconsideration of the December 21, 2000 approvable letter.

DISCUSSION:

After brief introductions of all participants, the teleconference began with the sponsor summarizing the purpose of the meeting. The Division Director explained that the Agency considers a teleconference a formal meeting and this meeting was not changed to a face-to-face meeting because it was felt the information could be handled sufficiently with a teleconference.

After reviewing the position paper, the Agency would consider accepting the patient level analysis not only for Myoview™, but for other myocardial perfusion agents as well. As far as the subsequent approvable action, the Agency still has concerns with the small sample size of the two pivotal studies. The Agency is additionally exploring other options with labeling, but these

would be addressed as review issues and need to be discussed with DDMAC. The sponsor asked when they could expect a response from the Agency regarding the possible options and whether this would be considered an official response or would the supplement need to be officially submitted. The Agency responded that we could have a response in about 3 weeks, but the application would have to be submitted before we could take an official action.

The Agency asked for clarification of how the sponsor intended to position Myoview™ in the market and whether they wanted a new indication or an extension of what is already approved. The sponsor responded that they would like to market the product as broadly as possible, but would probably only announce approval of the extended indication for pharmacologic stress. The FDA asked how Myoview™ would be positioned relative to other myocardial perfusion agents. The sponsor indicated that they would like a general indication for all populations. The Agency noted that the product was studied in a limited population and asked how that might affect promoting the product. The sponsor said that labeling for a limited population would be acceptable as long as it is not too restrictive.

The sponsor asked if there was any additional information that could be provided to the Agency to facilitate the review. Also, if the application is officially resubmitted as a complete response, what kind of timeline could be expected? The Project Manager explained that there are no PDUFA user fee goal dates for resubmission of efficacy supplements, however, per CDER policy, an internal goal date of 6 months would apply. The Division Director stated that no additional information is needed at this time and indicated that an official action would probably not take 6 months since we are familiar with the contents of the position paper and the results of the efficacy studies.

/s/

Patricia A. Stewart
Regulatory Project Manager

**DIVISION OF MEDICAL IMAGING AND
RADIOPHARMACEUTICAL DRUG PRODUCTS**

Industry Meeting Minutes

NDA: 20-372/SE-003
DRUG: Myoview (Tc99m Tetrofosmin for Injection)
SPONSOR: Nycomed Amersham Imaging
DATE: January 31, 2001

ATTENDEES:

Nycomed Amersham:

Daniel G. Mannix, Ph.D., Vice President Regulatory affairs
Joseph A. Pierro, M.D., Vice President Clinical Affairs
Robert Carretta, M.D., Senior Advisor Clinical Affairs

FDA:

Patricia Y. Love, M.D., M.B.A., Division Director
Sally Loewke, M.D., Division Deputy Leader
Patricia A. Stewart, Regulatory Project Manager

PURPOSE: To discuss the sponsor's basis for their request for the FDA to reconsider the decision presented in the December 21, 2000 action letter for NDA 20-372/SE-003 Myoview.

BACKGROUND:

Nycomed Amersham submitted an Efficacy Supplement February 26, 1999, that provided for the additional indication of Myoview used in conjunction with pharmacologic stress agents. The Agency has issued two approvable letters dated December 21, 1999 and December 21, 2000. The sponsor requested a meeting to discuss the basis of the action and a possible appeal. The Agency asked for clarification whether the sponsor's question was the December 21, 2000 action or if they had a scientific question with protocol. The sponsor explained .

_____ and would like the Agency to reconsider an approval for the limited indication based on how the product is utilized in the clinical setting. Also, the company is committed to the _____ study for the all comer indication.

DISCUSSION:

After brief introductions of all participants, the meeting began with the sponsor explaining their concerns that the clinical utility of Myoview (how the product is actually being used in a clinical setting) is not being reflected in the results of the studies. They explained that the clinical aspect of the perfusion study, the indication in patient management, is detecting myocardial wall defects versus a normal study. Small defects are not life threatening and would not indicate a cardiac catheterization study. Patients presenting with large defects and other symptoms need further evaluation and will be sent for cardiac catheterization. The Nuclear Medicine physician is more interested in reversible defects rather than the vessel level, which will be more important down the line prior to surgery. The decision to send a patient for a cardiac catheterization is not based entirely on a normal versus abnormal perfusion study. The cardiologist is guided not only by the visual assessment, but other risk factors as well. The blinded readers are being asked to determine whether the studies are normal versus abnormal with incomplete information.

The Agency acknowledged that it can be difficult to assess small lesions in the apex as well as to determine size and extent of regional differences and inquired how the clinical results of the perfusion study are reported. The sponsor responded that the clinicians look at both myocardial wall defects as well as the gated study. With questionable defects, they look for artifacts, microspasm, and at the family history to determine whether the patient will be sent for a cardiac catheterization. They do not expect the information obtained in a perfusion study to be equivalent to that obtained from cardiac catheterization. The sponsor said they were trying to understand the need for reporting vessel level versus regional or segmental and asked if the results could be viewed from only the patient level.

The Agency recognized that there would not be a one to one agreement in the analysis of vessel versus patient level, but were surprised that with a population having a high prevalence of disease, the correlation was so low. The sponsor explained that the literature reviews also showed poor correlation for other perfusion agents as well. Patients that are labeled as high probability may not necessarily belong in that category.

The Agency explained the dilemma in reconsidering the approvable action. The decision was not only based on the poor correlation of vessel versus patient level, but also that the trials were small and there were inconsistencies in the design. Even if the Agency reconsiders the decision based on how the drug is used in an actual clinical setting, there is still the problem of what to do with the small sample size. We suggested looking at the literature and publications from medical societies (i.e. American Society of Cardiology) to support a basis for reconsidering the studies from a patient level only perspective. The sponsor explained that the problem with the literature is most of the studies were done prior to FDAMA and do not follow current guidelines. The Agency acknowledged the dilemma and said the reviewers had done a literature search prior to the last approvable

action in hopes of finding additional support. Nevertheless, the sponsor may be able to identify relevant literature.

The Agency suggested that in order to consider how Myoview is used in a clinical setting, a sequential unblinded read may be appropriate and using the gated studies. The sponsor explained that gating was not obtained in the older studies, but gating is part of the clinical use now. The Agency asked how many patients were enrolled in the study and suggested an interim analysis. The sponsor responded that 220 patients were completed, but even though there was a high percentage classified in the >80% risk group, very few of those patients had cardiac catheterization. Also, the Agency stated that in order to do an interim analysis the sponsor would have to first prospectively define the end points, and then go back and retrospectively analyze the data. The sponsor expressed concern that the majority of the patients did not have cardiac catheterization and explained the patients with concomitant diseases such as diabetes, resulting in their placement in the high-risk category.

The Agency said the supplement could possibly be reconsidered with the submission of additional information supporting the claim that the clinical utility of the product is based on patient level analysis, though the labeling would have to reflect that the regional analysis was not documented. The caveat to this, however, is , the small sample size of the clinical trials. This is the greatest concern and appears to be unresolvable. If it is resubmitted on a patient level, the statistician will have to determine if numbers will be adequate even with a reanalysis. The sponsor asked if the small sample size would be overcome if they decide to do the interim analysis of the study and the Agency responded that we would have to consider what would be needed. A prospective plan of the interim analysis would need to be submitted for review. Reanalyzing the current studies on the patient level only and performing an interim analysis of the study are separate pieces. The sponsor stated that they could probably supply the information rather quickly and the Agency suggested a draft package be submitted for review.

The sponsor inquired about the appeal route and the Agency informed them that any new information would first be reviewed at the division level. The sponsor asked if the information supporting the actual clinical utility would be considered as a complete response. Since the information is an alternative to what was requested it would be considered a complete response if the numbers are adequate.

Cc:
Original NDA 20-372
HFD-160/Div. Files
HFD-160/Stewart/Loewke/Arnstein
HFD-715/Mucci

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-Physics, Inc.)
CATEGORY: Resubmission, response to approvable letter
SUBMITTED: June 28, 2000
PDUFA: December 28, 2000
COMPLETED: December 18, 2000

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

RELATED REVIEWS:

Clinical N Arnstein, MD, 12/08/99, 11/02/00
S Loewke, MD, 12/16/99, R Raman 12/20/00
Statistics T Mucci, PhD, 12/20/99, 11/07/00
Division Memo P Love, 12/20/99
Project Manager: P Stewart, BS

BACKGROUND

Myoview (Tc99m Tetrofosmin) Injection was approved in 1996 for the following indication:

"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."

Dosing regimen: As currently approved Myoview is provided as a kit containing dried components 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.

This efficacy supplement to expand the existing indication to include pharmacologic stress as a type of allowed myocardial stress was originally submitted on February 27, 1999. Initially the requested indication modification was to add the following sentence:

This request was to be supported with literature and with two small studies conducted by the sponsor. In an action letter of December 12, 1999 the application was considered as approvable with deficiencies that included a small sample sizes, consensus image interpretation, a less robust result in an enriched population, and insufficient literature support.

Therefore, the action letter requested the blinded re-read of the two clinical studies and the completion of a new clinical study. In addition to the efficacy letter indicated that a pediatric waiver was denied and that the agency would consider a request for deferral. Also, additional financial disclosure data were requested. The pediatric and financial disclosure assessments will be addressed at the end of this memorandum.

After a meeting with the sponsor about the efficacy determination, the sponsor completed the blinded re-read of the originally submitted studies of the enriched population of patients, and is conducting a new study in a larger population in a clinically relevant setting. In the interim, the current submission requests the consideration of a more restricted indication based on the blinded re-read and a reconsideration of the literature. The sponsor re-evaluated the previously submitted literature and new articles published since the original application. Of these the sponsor identified a core of articles. These included 5 that were originally submitted, 3 articles that used unapproved pharmacologic stress agents and 1 article that reported the results of the sponsor's 2 studies before the blinded re-read. The sponsor concluded that none of the articles alone would provide robust information. However, collectively, the articles should be considered as strongly supportive.

Summary of Reviewer Findings: All three reviewers noted the challenge of evaluating a drug to identify differences in perfusion in the context of coronary artery disease. Historically, the agency standard for detecting coronary artery disease in iodinated contrast angiography. The first perfusion agents were approved if the identified abnormalities correlated with regions supplied by the vessels that had coronary artery disease on angiography. Because of anomalous vascular supply, these correlations are not perfect. Therefore, in some products, the presence of myocardial infarction was confirmed by other methods; in others the patient level analysis was the predominant factor reported in the labeling. Also, after the approval of the first myocardial perfusion agent, most clinical trials included thallium as an active control. In trials with active controls, despite similar test statistics, typically the control and the test agent do not have 1:1 correlation.

The two studies under re-read did not include a method to confirm the presence or absence of myocardial infarction. They did correlate differences in perfusion with the region of coronary artery disease identified on rest and pharmacologic stress. These two studies are identified as P53-006 and PR95-302. In both studies the standard of truth was iodinated contrast conventional angiography. An active control was included in study PR95-302 only. As noted in the 1st review cycle, both studies enrolled very enriched populations. Study P53-006, evaluated 49 patients with known or suspected coronary artery disease and a retrospective prevalence of 78% coronary artery disease¹. Study PR95-302 blindly evaluated 19 patients with previously identified >50% stenosis on angiography (i.e., a 100% prevalence of disease). The patients did not have a clinical indication for imaging. The fact that the populations are enriched is the basis of their request for an indication focused on these patients.

¹ Note that my original review identified the prevalence as 92%. This is an error.

These data were reviewed by the clinical reviewer, clinical team leader, and statistical reviewers with different recommendations, respectively, of either 1) continued approvable pending acceptable data from the ongoing study, 2) approval with a limited indication, or 3) lack of a definitive recommendation but with the assessment of similar ability to detect coronary artery disease. The data are not presented in a manner to determine if Myoview is detecting the known disease or new abnormalities. All reviewers considered the method of blinded re-read and majority analysis as acceptable. The concerns identified by the different reviewers are briefly summarized in the following paragraphs.

The clinical review noted that the letter requested a blinded re-read with results that were at least as robust as the consensus read. Also, the review considered the quality of the new literature articles. The review identified the following deficiencies:

1. Small sample size (P53-006 n = 49) (PR95-302 n = 21) These numbers are smaller than those available in the original consensus read and they decreased further for different subset analyses (single vs. multiple vessels)
2. Lower sensitivity (vs. Thallium in study PR95-302)
3. Lower sensitivity (vs. the original consensus read of P53-006 and PR95-302)
4. Sensitivities lower than expected for an enriched population
5. Poor scan quality (47%, 15%, 15% considered to be optimum by blinded readers PR95-302 and 65%, 67%, and 77% for P53-006).

The clinical team leader and the statistician additionally considered 1) whether the test statistics were similar to that of the original Myoview and thallium approvals and 2) whether the confidence intervals in the PR95-302 study were overlapping. Both reviewers note that the subject level results were predominant in the original Myoview and that in the re-read the subject level sensitivities were similar. Also, both reviews note that the strength of the comparator database on a vessel level is similar to that of the original Myoview approval (e.g., number of vessels evaluated in comparison to thallium). The following tables summarize the statistical characteristics. The first column is the sample size and the blinded reader number. The next 2 columns report the sensitivity and specificity. The last 2 columns report the prevalence of disease and its associated positive and negative predictive values. Based upon this, at the patient level Myoview performs best in sensitivity and positive predictive value.

These blinded re-read results demonstrate consistency in 2/3 readers for the patient level test statistics. Depending upon the study, by 2 of 3 blinded readers, the sensitivity ranges from 70 to 83%. In study 306, the positive predictive value ranges from 85-90%. These values are consistent with those of the original Myoview approval for exercise induced stress. The specificity and negative predictive values are in the range of 45-54%. Thus, their clinical role in ruling out disease is limited. [The predictive values and specificity were not calculated for study 302, since all enrolled patients had entry requirement angiographic evidence of disease.]

Table 1: P53-006 Patient Level Blinded Re-read Results				
N = 49	Sensitivity	Specificity	Prevalence of Patient Disease = 78%	
			PPV	NPV
Reader 1	81.6 %	54.6 %	86.1 %	46.2 %
Reader 2	83.3 %	50.0 %	85.7 %	45.5 %
Reader 3	47.4 %	81.8 %	90.0 %	31.0 %
Derived from Dr. Arnstein's review page 11				

Table 2: PR95-302 Patient Level Blinded Re-read Results				
N = 19	Sensitivity	Specificity	PPV	NPV
Reader 1	74%	Can not calculate with prevalence of 100%		
Reader 2	70%			
Reader 3	76%			
Derived from Dr. Mucci's review, page 15, appendix, table 2, sponsor results				

On a vessel level, the sensitivity and positive predictive values are briefly summarized in the following tables that are derived from Dr. Arnstein's review. The sensitivity results are best for the right coronary artery (RCA) and worse for the left anterior descending (LAD). These demonstrate that, with the exception of the RCA with results in the 70% range, the left anterior descending and left circumflex (LCx) majority results range from 40 - 56%. These results are consistent with chance alone. The positive predictive values, as expected, are high in the 100% prevalence study. However the highest values are for the LAD, not the RCA. Dr. Mucci's review presented a composite statistic for all vessels (shown in column 5 as the average). The averages produced a lower overall sensitivity and specificity.

Table 3: P53-006 Vessel Level Blinded Re-read Results								
	Sensitivity				Positive Predictive Value, Prevalence of Vessel Disease = 46 %			
	LAD (n= 49)	LCx (n = 49)	RCA (n=49)	Average (n=149)	LAD (n= 49)	LCx (n = 49)	RCA (n=49)	Average (n = 147)
Reader 1	44.4 %	35.0 %	76.2 %	51%	80.0	70.0	66.7 %	41%
Reader 2	56.0 %	52.6 %	75.0 %	56%	70.0	69.0	53.6 %	35%
Reader 3	29.6 %	40.0 %	42.9 %	37 %	100%	72.7	64.3 %	50%
Derived from Dr. Arnstein's review page 13; Average values from Dr. Mucci's review page 10								

Table 4: PR95-302 Vessel Level Blinded Re-read Results								
	Sensitivity				Positive Predictive Value, Prevalence of Vessel Disease = 77 %			
	LAD (n= 19)	LCx (n = 19)	RCA (n=19)	Average (n=57)	LAD (n= 19)	LCx (n = 19)	RCA (n=19)	Average (n = 57)
Reader 1	40.0%	33.3%	71.4%	51 %	100%	100%	83.3%	82 %
Reader 2	31.3%	43.8%	53.3%	61 %	100%	100%	80.0%	65 %
Reader 3	52.9%	41.2%	66.7%	37 %	100%	100%	71.4%	90 %
Derived from Dr. Arnstein's review page 21; Average values from Dr. Mucci's review page 11								

Literature: Of the 9 articles identified as critical by the sponsor, 5 were evaluated during the first review cycle. (of these none were considered to be strongly supportive and their deficiencies were stated in the original approvable letter). Of the remaining 4 articles, 1 is the literature report of the sponsor's studies before the blinded re-read, and 3 new articles used unapproved pharmacologic stress agents. Therefore, the literature assessment is still considered to be supportive but not sufficient.

Assessment: In considering these recommendations, on a patient level the sensitivity and positive predictive values suggest clinical usefulness. However, the vessel sensitivities are much lower and vary with the vessel. Clinically, the vessel level evaluation is important to the regional evaluation of myocardial perfusion. Even in the studied high prevalence populations the clinical benefit of using Myoview is not clear.

Overall, the deficiencies identified in the original approvable letter remain and to some extent are amplified. The letter indicated that the literature deficiencies could not be overcome and the new articles contained the same deficiencies as those submitted during the 1st review. For the sponsor's two studies, the sample size was identified as being small. Based upon the data lost during the re-read the sample sizes are smaller. Interestingly the letter requested a more robust result in comparison to the consensus read. In one respect the results are more robust because of the similarity between 2 independent blinded readers. On the other hand the results are less clinically useful because of the lower sensitivities.

Collectively these two small studies (one in a non-clinically relevant population) provide pharmacodynamic evidence of Myoview's ability to detect differences in perfusion on a patient level. Its needed clinical usefulness in regions associated with vessel disease has not been demonstrated. Because of the weakness of the literature database, the literature can not resolve the deficiencies of the sponsor's studies. Hence, these data marginally support expansion of the indication to a limited population. Therefore, this application remains approvable pending acceptable results from the ongoing larger study.

Additionally, because of the noted difficulty in analyzing these data, the new study should include an active control and should be performed in a clinically relevant setting. The purpose for the study should be clearly identified (e.g., to determine suitability for therapeutic

intervention, extension of disease, ischemia vs. infarct). These requests were identified in the original approvable letter and this approach is consistent with current recommendations for this type of study.

SAFETY UPDATE: Acceptable. See Dr. Arnstein's review page 36

C. Pediatric use:

In response to the division's request for a deferral of pediatric studies for the pharmacologic stress indication, the submission contained a deferral request until pharmacologic stress agents are approved for use in the pediatric population. This is considered to be reasonable and the studies are deferred until 5 years after the approval of such agents in pediatric patients.

In addition, the Myoview NDA has a phase IV commitment to develop information for dose adjustment in pediatric patients. During the review of the resubmission, Nycomed submitted a request for 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. Additionally, the article discusses the need for institutions to develop an approach for pediatric patients. Drug specific considerations are not addressed.

These data are not sufficient to support the development of pediatric labeling for Myoview. The original phase IV commitment for dose adjustment would require an assessment of both the radioactivity 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.

D. Financial disclosure

During the original review cycle, the application did not contain the financial disclosure forms of the blinded readers. These were requested in the action letter. These were not included in the current submission because the sponsor felt that under 21 CFR 54.2(d) this applies to the onsite investigators who are directly involved in the treatment or evaluation of research subjects. Because of the nature of imaging trials, the research subject evaluations that provide the basis for efficacy are provided by the blinded image readers. In effect these readers are surrogates for the onsite investigator. They not only influence the overall results of the trial, but they provide much of the most meaningful, relevant efficacy information. Therefore, the financial disclosure forms are needed from these evaluators. These data will be requested again.

ACTION:

1. Continued approvable
2. Note denial of pediatric waiver
3. Repeat request for financial disclosure information for blinded readers

PS - 12/20/00
~~Patricia Y. Love, MD~~
Patricia Y. Love, MD
Director, Division of Medical Imaging &
Radiopharmaceutical Drug Products

**DIVISION OF MEDICAL IMAGING AND
RADIOPHARMACEUTICAL DRUG PRODUCTS**

Industry Meeting Minutes

NDA: 20-372/SE-003
DRUG: Myoview (Tc99m Tetrofosmin for Injection)
SPONSOR: Nycomed Amersham Imaging
DATE: February 17, 2000

ATTENDEES:

Nycomed Amersham:

Joseph A. Pierro, M.D., Vice President Medical and Clinical; Acting Vice President
Regulatory Affairs
Judith Murphy, M.D., Senior Director, Medical Affairs
Rocco Ballerini, Director, Biostatistics
Mary Ellen Smirich, Biostatistician

FDA:

Patricia Y. Love, M.D., M.B.A., Division Director
Robert K. Leedham, Jr., Associate Director
A. Eric Jones, M.D., Medical team Leader
Sally Loewke, M.D., Medical Team Leader
Nelson B. Arnstein, M.D., Medical Officer
Anthony Mucci, Ph.D., Mathematical Statistician
Rubynell Jordan, Acting, Supervisory Consumer Safety Officer
Archana Reddy, Regulatory Project Manager
Patricia A. Stewart, Regulatory Project Manager

PURPOSE: To discuss the approvable action letter dated December 21, 1999, and the proposed independent blinded reread of completed studies P95-302 and P53-006, as well as the proposed new study

BACKGROUND:

Nycomed Amersham submitted an Efficacy Supplement that provided for the additional indication of Myoview used in conjunction with pharmacologic stress agents. The supporting studies submitted had several protocol design flaws, including the lack of independent blinded reading. The Agency suggested that the sponsor reread images in the pivotal studies and submit an additional supporting study including patients from a "non-enriched population". The sponsor submitted draft protocols for independent blinded rereads of protocols 53-006 and 95-302 and a new pivotal study to support the proposed indication.

DISCUSSION:

After brief introductions of all participants, the meeting began with a slide presentation by the sponsor (Attachment I) and discussion of the requirements necessary to obtain an approval action. The FDA informed the sponsor that the agenda that was submitted for the meeting was very broad and we would probably not be able to resolve all the issues at this meeting.

The first agenda item was the use of literature as supportive data. The Division Director explained that the Agency used the criteria defined in the guidance's "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" and "Developing Medical Imaging Drugs and Biologics" to determine the acceptability of the articles. The methods section is reviewed to determine whether the protocol contained such key elements as a blinded read, whether the study was done prospectively, if there is a clear basis for their conclusion, and if the results are based on the perspective statistical plan. The sponsor asked if literature could be used to support safety data. The Director responded that more often literature is not used to support safety because most articles do not discuss safety in detail. However, if safety literature data were available it would be considered.

Blinded Read Protocol for P53-006 and PR95-302:

The medical officer noted that the studies were different because only one study used Thallium as a comparator and asked whether the Thallium studies would be reprocessed and read. The sponsor responded that the Thallium studies would be reprocessed and read in the same way the Myoview images would be at the core lab. The medical reviewer was concerned that only 2 of 3 axes were to be reported. The sponsor explained that the readers will view all three axes but the number of segments to be scored will be reduced, which is standard practice. They will use a 17 segment model for scoring as recommended by the American Nuclear Cardiology Society. The medical officer pointed out that the number of segments assessed in the original 2 supporting studies were not the

same. The sponsor stated that the reanalysis would use the same 17 segments for both studies as well as the Thallium studies.

The medical officer asked if they would create polar maps when the images were reprocessed and if this information would be provided to the readers. The sponsor responded that the blinded readers would be provided with the raw data in DICOM format, all 3 axes, and the polar map (for visual assessment only). The software will be standardized and identical except for the European study. The same results should be obtained though, since the processing will be done on the same type of computer.

The Agency asked if the blinded reread could be done without reprocessing. The sponsor explained that the data must be reprocessed because only the raw data was archived. The consensus read was done using digital images and only some of the paper copies of the processed images are available now. The Agency asked that the differences in the consensus read vs. the blinded reread be provided in a side by side comparison, as well as justification for the differences (i.e. image processing, CFRs, statistical plan, number of segments, definitions of normal vs. abnormal). The sponsor agreed to provide the requested information and further explained that they will use guidelines from the ASNC for the reconstruction parameters and there will be 3 independent blinded reviewers for each study who have no knowledge of the patient history or the protocol.

The statistics reviewer expressed concern that previously paired reads were done using rest and stress images to assess quantifying perfusion, whereas now they are proposing scoring the images and wondered if it would be the same. The sponsor said that the scores would be assigned to each segment and calculated independently, and even though the readers would be provided with maps and quantitative information, the final interpretation would be visual, not quantitative.

The medical officer asked for clarification why in evaluating individual defects, if one segment is abnormal it is considered normal instead of equivocal. The sponsor explained that smaller segments are not prognostically important and reflect a low risk population. A segment will be categorized as normal if one or no defect is seen, and considered positive if seen on two views.

The FDA explained that the results of the blinded read must be more robust than the previous data ~~both~~ on a subject and vessel level for the proposed restricted labeling to be considered. The sponsor explained that in cases where there are vessels with major disease, it is sometimes harder to identify individual vessels because of collaterals or anatomical variations. The sponsor asked how it would be weighted if both agents (Thallium and Myoview) have poor vessel level results. The Agency acknowledged that Thallium is not always accurate but said the data from the blinded read would have to be better than the data from the consensus read. Overall the requested information is needed before deciding on the adequacy of the data

The sponsor will submit the proposed changes for review.

Redacted 1

pages of trade

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confidential

commercial

information

Pediatric Studies:

A request for deferral of studies will be submitted based upon the fact that no pharmacologic stress agent is approved yet for pediatric use.

Phase 4 Commitments for original NDA:

The request for human metabolic and pharmacokinetic profile and pediatric studies will be addressed separately.

ACTION:

The sponsor will submit the following requested information for review before initiating the study:

- Proposed labeling anticipated to be supported by this study
- Entry criteria for categorization into low, mid, and high likelihood of disease groups
- Truth panel criteria at the end of the study
- Training of blinded readers and scoring methods to be used by the blinded readers

- Identify blinded readers
- Review primary endpoint calculations for intermediate group
- Submit additional data supporting the higher 1 and 2 day dose and dosing regimen

Cc:
Original NDA 20-372
HFD-160/Div. Files
HFD-160/Stewart/Loewke/Arnstein
HFD-715/Mucci

DEPUTY DIVISION DIRECTOR CLINICAL REVIEW of NDA 20372
AND
DIVISION MEMO TO THE FILE

NDA: 20372
DRUG: Myoview (Tc99m Tetrofosmin)
ROUTE: Intravenous
MODALITY: Single Photon Emission Tomography
INDICATION: Pharmacologic Stress Perfusion Imaging
SPONSOR: Amersham Health
CATEGORY: Resubmission
SUBMITTED: May 23, 2001
6 MONTH: November 23, 2001
COMPLETED: November 4, 2001

RELATED DRUGS: Thallium-201, Cardiolite®

RELATED REVIEWS:

Clinical: N. Arnstein, M.D. 12/08/99, 11/02/00
S. Loewke, M.D. 12/16/99, R. Raman, M.D. 12/20/00
Statistics: T Mucci, PhD. 12/20/99, 11/07/00
Division Memo: P. Love, M.D. 12/20/99, 12/18/00
Project Manger: Patricia Stewart

BACKGROUND:

Myoview is a radiopharmaceutical that is administered intravenously for purposes of imaging myocardial perfusion. Myoview was originally approved in 1996 for the following indication:

Myoview is indicated for the 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.

The Sponsor submitted an efficacy supplement in February of 1999 to add pharmacologic stress to the existing indication. This submission cited two clinical trials and literature as the basis of their proposed labeling changes. Review of this supplement resulted in the issuance of an Approvable letter on December 12, 1999. The Approvable letter cited the following major deficiencies: small sample size, consensus image interpretation, an enriched population and insufficient literature support. The letter proceeded to request a blinded re-read of the two clinical studies and completion of a new clinical study.

On June 28, 2000, an efficacy supplement responding to the December 12, 1999 Approvable letter was submitted. In this submission, the Sponsor included the blinded re-read data that had been requested and a re-evaluation of the literature. Based on this data, the Sponsor requested consideration of the following restricted indication (changes in bold) in the absence of the requested additional clinical study.

DRAFT
LABELING

In response to this resubmission, an Approvable letter was issued on December 21, 2000. This letter cited the following major deficiencies: insufficient literature support and poor vessel level sensitivity in a patient population with a high prevalence of disease. The Division stated that the clinical relevance of the poor vessel level results in regional perfusion assessments remained unclear and it was requested that the Sponsor complete the ongoing clinical study.

Following issuance of the December 21, 2000 Approvable letter, the Sponsor requested a meeting with the Division for reconsideration of the Approvable action. A meeting was held on January 31, 2001 during which the Sponsor requested reconsideration of the limited indication based on the fact that the subject level analysis, as opposed to the vessel level analysis, provides the imaging results that are considered clinically relevant. Thus, on May 23, 2001 the Sponsor submitted an efficacy supplement requesting reconsideration of the limited indication. The submission consists of literature articles that discuss the clinical utility of myocardial perfusion imaging, testimony of four clinicians and literature comparing the efficacy of Myoview to Sestamibi. Also contained in this resubmission are a financial disclosure statement and a safety update. The format of this review will follow the above order with the exception of the issue of the comparability of Myoview to Sestamibi. This issue was not raised in any of the approvable letters by the Division and the Sponsor is not proposing any labeling changes based on this literature, therefore this literature will not be discussed in this review.

The purpose of this review is to determine whether the literature data submitted adequately supports the clinical utility of the patient level image results alone. Since the literature deals with more than just this topic, the focus of the literature review will be strictly from the vantage point of radionuclide myocardial perfusion agents and their role in clinical practice. In addition, since the Sponsor's trials enrolled only those patients with known or suspected coronary artery disease (CAD), this review will only focus on the use of myocardial perfusion imaging in patients with stable CAD. Therefore, this review will not discuss the role of myocardial perfusion imaging in the clinical setting of acute myocardial infarct, unstable angina, myocarditis etc.

Two articles have been identified as lead articles by this reviewer. The two articles are as follows:

Guidelines for Clinical Use of Cardiac Radionuclide Imaging, Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), Developed in Collaboration with the American Society of Nuclear Cardiology JACC 1995 Vol 25, No. 2:521-47.

Imaging Guidelines For Nuclear Cardiology Procedures Part 2
J Nuclear Cardiology 1999:G53-G84.

These articles have been chosen because they provide guidelines, published by large authoritative medical societies that discuss the clinical relevance of radionuclide myocardial perfusion imaging and the appropriate method of reporting such imaging results.

In the clinical guideline, the ACC/AHA task force states that radionuclide imaging has value in the diagnosis and risk stratification of patients with coronary artery disease. The number, size and location of perfusion abnormalities on stress imaging have relevance as they reflect the location and extent of functionally significant stenosis. The task force identified that the most consistent predictors of cardiac death or nonfatal myocardial infarction appear to be the number of transient perfusion defects seen on perfusion imaging regardless of the type of stress employed (i.e exercise or pharmacologic). Although they state that most of the supporting data stems from Thallium-201 myocardial perfusion imaging, it is felt that Thallium-201 and Tc-99m Sestamibi could be used interchangeably based on similar diagnostic accuracy findings¹. The task force reports the average values of sensitivity and specificity for exercise Thallium-201 SPECT imaging to be 89 and 76% respectively.

Reiteration of the predictive value of transient myocardial perfusion defects can be found in other supportive literature articles provided by the Sponsor^{2,3}. Other variables such as lung uptake and ventricular dilatation have also been identified as having predictive value.

¹ While this may be reasonable in patient care, in clinical trials drugs with similar accuracy may have different sensitivity and specificity values in the same patient.

² Brown et al. Prognostic Value of Myocardial Perfusion Imaging: State of the Art and New Developments, J Nuc Cardiology; 3:516-537, 1996.

³ Brown et al. Prognostic Value of Thallium-201 Myocardial Perfusion Imaging, Circulation; 83: 363-381, 1991.

Also noted in several articles was the prognostic value of a normal myocardial perfusion study. It has been shown that normal myocardial perfusion imaging carries a benign prognosis^{1,2}. Meaning, the annual event rate of future death or myocardial infarction in a patient population with normal myocardial perfusion imaging was found to be similar to that of the general population. In addition, Brown et al postulates that the prognosis continues to be benign even in the presence of exercise electrocardiographic and angiographic markers of poor outcome. Thus, it appears that the hemodynamic effects of coronary artery disease have greater importance than the anatomic findings alone.

Although not highlighted as part of the clinical guidelines, several articles also provide clinical algorithms for the diagnostic evaluation of coronary artery disease^{4,5}. These algorithms suggest that the subject level results of myocardial perfusion imaging have impact on clinical management of patients.

The review will now focus on the standard method of reporting the results of myocardial perfusion imaging. In theory, the value of any diagnostic test should be represented by the information reported by the interpreting physician. This information is in turn used by the referring physician to make relevant decisions about patient management.

The imaging guidelines for Nuclear Cardiology Procedures were published in the Journal of Nuclear Cardiology in 1999. These guidelines delineate for the Nuclear Medicine Physician those relevant image parameters that should be assessed and reported as part of their standard image interpretation for a myocardial perfusion study. Although there are a variety of parameters that the physician should address (technical quality, ventricular dilatation assessment, lung uptake assessment, non-cardiopulmonary uptake, and perfusion defect assessment including reversibility), as part of the assessment of a non-gated SPECT study, the parameter most relevant to the purpose of this review is how perfusion defect information data is reported. For this parameter, the guidelines propose that a perfusion defect should be characterized by its location and its extent/severity. From the standpoint of location, it is recommended that the assessment be made with relationship to specific myocardial walls, that is, apical anterior, inferior and lateral. These wall designations are further divided into segments. These segments have been associated with coronary artery territories, however, the imaging guidelines warn against this approach to interpretation, as vagaries in coronary anatomy are common. Defect severity and extent can be assessed qualitatively, semi-quantitatively or quantitatively. The guidelines state that qualitative approach is standard however the semi-quantitative assessment is preferred. The guidelines further state that a consistent approach to assessing defect extent and severity is clinically important as both of these variables contain independent prognostic power. In addition to individual segmental scoring, the guidelines recommend that summed scores be calculated for stress and rest images and that a difference score be calculated.

⁴ Cacciabauda and Hachamovitch. Stress Myocardial Perfusion SPECT in Women: Is it the Cornerstone of the Noninvasive Evaluation?, J Nuc Medicine;39:5; 756-759, 1998.

⁵ Shaw et al. Clinical and Economic Outcomes Assessment in Nuclear Cardiology. Q J Nuc Medicine; 44: 138-152, 2000.

Reversibility of myocardial perfusion defects should be categorized qualitatively as partial or complete. The physician's overall interpretation should take into account all the parameters evaluated as part of their image assessment.

The Sponsor has also submitted statements from 2 Nuclear Medicine Physicians and 2 cardiologists with special training in Nuclear cardiology. The statements from these four physicians reiterate that the value of a myocardial perfusion study is based on the presence and extent of a perfusion defect. They also agree that due to vagaries in coronary vessel anatomy, the most relevant means of reporting perfusion defects is by geographic region (myocardial wall). Both Cardiologists state that the prognostic value of myocardial perfusion imaging aid in their patient management decisions.

DISCUSSION:

Historically the method of study for this class of diagnostic drugs relied heavily on the ability of the product to show the presence of a myocardial perfusion defect in association with a regional presence of coronary artery stenosis on angiography. It is clearly understood that this comparison is not perfect as radionuclide imaging delineates the physiological consequences of the stenosed vessel and angiography merely identifies the anatomic presence of the stenosis. Likewise, anomalous vessel supply and collateral circulation precludes a direct correlation. Therefore, the perfusion results of the test agent are typically compared with an active control, Thallium-201. However, within the same patient the perfusion results for the test drug and comparator frequently are not the same. Therefore, the angiogram results are needed to document the diagnosis of CAD. This typifies the inherent difficulty of identifying regional perfusion defects.

Today there is significant impetus by the Agency to insure that the clinical utility of all drugs, therapeutic and diagnostic, be provided at the time of drug approval. Therefore, if we are going to change from relying on both subject and vessel level results to subject level results alone (in the context of having documented CAD in any vessel), there must be clinically relevant justification for such a change. This requires information on how the subject level data alone is used in a relevant clinical setting.

Myoview was originally approved in 1996 for a rest/exercise myocardial perfusion claim. Before and since this approval there has been extensive literature documentation of the clinical relevance of this class of radionuclide diagnostic drugs. In fact, as stated earlier, the value of radionuclide imaging stems from its ability to identify transient perfusion defects. The value of identifying the extent and severity of these defects appears to impact the treating physician's decision-making ability from the diagnostic and therapeutic management point of view. Thus the subject level assessment of radionuclide myocardial perfusion imaging appears to provide the most relevant clinical data to the practicing physician. This conclusion is specific to radionuclide imaging. The extent to which this applies to other imaging modalities that may provide additional anatomic information is not clear at this time.

In the context of a drug with prior exercise stress approval, as in the case of Myoview, the amount of data needed to support the addition of pharmacologic stress warrants further discussion. Previous approval for exercise induced stress, in theory, has defined how the test drug distributes when administered under rest and stress conditions. Therefore, although pharmacologic stress agents function differently from exercise in producing that stress, the bottom line is that they both have been shown to illicit stress induced ischemia in patients with significant CAD. Whether exercise induced stress is equivalent to that of pharmacologic induced stress is not addressed by this review. Regardless of the method of stress, it is expected that Myoview would perform in a similar manner, unless there is interaction between the pharmacologic stress agent and the imaging test drug itself. Therefore, there is need for both safety and efficacy data on the co-administration of these drugs. Thus, a brief look at the subject level findings of the re-read data will follow.

The subject level re-read data from the two small clinical trials (PR95-302 and P53-006) provide sensitivities (for two out of three readers) within the range of 68-82% (See Dr. Mucci's review Tables I and II). As stated by Dr. Mucci, these subject level sensitivities are similar to those of the original exercise approval, however, no conclusions about specificity can be made due to sample size limitations. Thus Dr. Mucci proposes that any indication granted for pharmacologic stress would need to emphasize the enriched nature of the population studied. I agree with his assessment and recommend that prevalence values for both studies be reported in the clinical trials section of the label. Also, these sensitivities were found to be weaker than those of Thallium-201, therefore the Thallium-201 comparator data should be included in the label. With regards to the reversibility of the imaged perfusion defect, the Sponsor provided limited data with Thallium-201 as a comparator. This data shows the percent agreement of 53-67% (across readers) for identifying subject level reversibility with respect to Thallium-201 (See Dr. Arnstein's review dated 11/3/2000, Table 5.39). This data is also recommended for the label.

SAFETY UPDATE:

The safety update provided covered the period between June 1, 2000 to May 1, 2001. During this period, the Sponsor reports that [redacted] were sold world wide thus assuming approximately [redacted] exposures. There were 42 adverse events reported in 28 patients. Three of these adverse events were reported as part of ongoing clinical studies and the remainder were reported as spontaneous reports from US and non-US sites. A total of 6 serious adverse events (Table 1) were reported (3 from clinical trials and 3 from spontaneous reports).

Table 1: Serious Adverse Events

Patient ID	Pharm. Stress	AGE	SEX	EVENT	LATENCY	OUTCOME
ES*		80	F	Hemorrhage rectum	1 day	Ongoing
RR*	+	70	M	Respiratory arrest	3 minutes	Recovered
LS*	+	68	F	Cerebrovascular disorder convulsions	4 hours	Unknown
MAW†		44	M	Syncope	5 days	Recovered
RLL†	+	86	F	Tachycardia	27 hours	Recovered
WSB†	+	68	M	Chest pain	19.5 hours	Recovered

*Spontaneous reports, † Clinical trial reports, Source: Sponsor Tables 1 and 21 (vol. 4).

From the narratives provided, all of the clinical serious adverse events appear to be unrelated to Myoview administration. Of the 3 serious spontaneous reports, the patient who developed respiratory arrest also was given adenosine as a pharmacologic stressor. It is unclear what past medical history this patient had, however, the narrative states that this patient used his albuterol inhaler just prior to adenosine dosing suggesting some type of respiratory problem. For the first three minutes of adenosine infusion, the patient was asymptomatic and Myoview was administered. Within approximately 4 minutes into adenosine infusion and 1 minute post Myoview administration, the patient began to have respiratory symptoms (cough). The patient subsequently went into respiratory arrest. The patient was treated and fully recovered. Attribution of this adverse event to the administration to adenosine appears plausible as adenosine has been known to cause bronchoconstriction. However, given the onset of symptoms within one minute of Myoview administration, it is recommended that this serious adverse event be described in the label with appropriate mention of the concurrent use of adenosine.

The patient who experienced the cerebrovasuclar disorder also had the co-administration of dipyridamole as a pharmacologic stressor. The narrative states that this patient experienced nausea and "illness" within 3 hours of receiving Myoview and dipyridamole. The next day, the patient experienced seizures and was admitted to the hospital. The patient's outcome was not reported. The reporting physician attributed this patient's seizures to cerebral ischemia related to the hypotension brought about by dipyridamole administration. Transient cerebral ischemia, has been described in the warning section of the dipyridamole label. Given the timing of the serious event (seizures) and the co-administration of dipyridamole, it appears unlikely that this event is related to Myoview administration.

Of the non-serious adverse events, the most frequently reported event was allergic reaction reported in 14 out of 22 patients. Reviewing the spontaneous reports, the majority of the cases of allergic reaction were reported as rash/hives. There was one case of swelling of the lips and tongue seen 1 hour post-Myoview injection.

Given the exposure to be approximately _____ patients, the incidence of allergic reaction is small and has already been reported in the Myoview label at the time of its original approval.

Overall the safety profile seen in the update does not appear to show any particular trends suggesting the need for changes to the warnings or precautions section of the label.

FINANCIAL DISCLOSURE:

The Sponsor has provided a certification of financial interests for the 6 investigators who performed the blinded re-read of the two clinical studies.

CONCLUSIONS:

Overall, the subject level results of these two small trials when combined could serve as the basis of approval given the fact that there is previous exercise approval data and years of clinical experience with this drug. Thus, there is adequate evidence to support the safe and efficacious use of Myoview for identifying myocardial perfusion defects in patients with known or suspected coronary artery disease when used with pharmacologic stress.

RECOMMENDATION:

Approval

**APPEARS THIS WAY
ON ORIGINAL**