CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-150 / S-019

Name:	Thallous Chloride Tl-201 Injection
Sponsor:	Mallinckrodt, Inc.
Approval Date:	July 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-150/SE 019

Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Dear Dr. Brodack:

Please refer to your supplemental new drug application (NDA) dated September 29, 2003, received September 30, 2003, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Thallous Chloride T1-201.

We acknowledge receipt of your submissions dated September 29, and December 19, 2003, March 2, and 10, June 11, and July 8, 2004.

This supplemental new drug application proposes for the use of Thallous Chloride T1-201 as a myocardial perfusion imaging agent, in combination with the approved pharmacologic stress agents, for a pharmacologic stress indication.

We completed our review of this application, as amended, 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:

"Thallous Chloride Tl-201 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 and who cannot exercise adequately."

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 18-150/SE1 019**." Approval of this submission by FDA is not required before the labeling is used.

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. We are deferring submission of your pediatric studies for ages less than 18 years until 5 years after the approval of any pharmacologic stress agents in pediatric patients in the United States.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for using Thallous chloride Tl 201 for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress in pediatric patients less than 18 years of age.

   Final Report Submission: We are deferring submission of your pediatric studies until 5 years after the approval of any pharmacologic stress agents in pediatric patients in the United States.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

If you have any questions, call Diane C. Smith, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}
George Q. Mills, 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 Labeling

ATTACHMENT
(Agreed Draft Labeling)

APPEARS THIS WAY
ON ORIGINAL

Thallous Chloride Tl 201 Injection

Rx Only

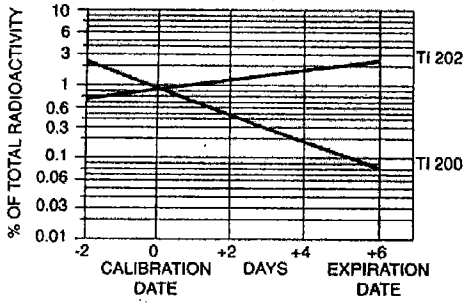
Diagnostic—For Intravenous Use

DESCRIPTION

Thallous Chloride Tl 201 Injection is supplied in an isotonic solution as a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous administration. Each milliliter contains 37 megabecquerels (1 millicurie) Thallous Chloride Tl 201 at calibration time, made isotonic with 9 milligrams sodium chloride and preserved with 0.9% (v/v) benzyl alcohol. The pH is adjusted to between 4.5 to 7.0 with hydrochloric acid and/or sodium hydroxide. Thallium TI 201 is cyclotron produced. At the time of calibration it contains no more than 1.0% Thallium Tl 200, no more than 1.0% Thallium Tl 202, no more than 0.25% Lead Pb 203, and no less than 98% Thallium Tl 201 as a percentage of total activity. No carrier has been added.

It is recommended that Thallous Chloride Tl 201 be administered close to calibration time to minimize the effect of higher levels of radionuclidic contaminants present at pre- and post-calibration dates. The concentration of each radionuclidic contaminant changes with time. Figure 1 shows maximum concentration of each radionuclidic contaminant as a function of time.

Figure 1. Radionuclidic Contaminants



PHYSICAL CHARACTERISTICS

Thallium Tl 201, with a physical half life of 73.1 hours, decays by electron capture to mercury Hg 201.[1] Photons that are useful for detection and imaging are listed in Table 1. The lower energy x-rays obtained from the mercury Hg 201 daughter of thallium Tl 201 are recommended for myocardial imaging, because the mean percent disintegration at 68.9 to 80.3 keV is much greater than the combination of gamma-4 and gamma-6 mean percent disintegration.

Table 1. Principal Radiation Emission Data[1]

Radiation	Mean % Per Disintegration	Energy (keV)
Gamma-4	2.7	135.3
Gamma-6	10.0	167.4
Mercury x-rays	94.4	68.9–80.3

[1]Kocher, David C., "Radioactive Decay Data Tables," DOE/TIC- 11026, 181 (1981).

EXTERNAL RADIATION

The specific gamma ray constant for thallium Tl 201 is 4.7 R/mCi-hr* at 1 cm. The first half-value thickness of lead (Pb) is 0.0006 cm. A range of values for the radiation emitted by this radionuclide with the corresponding exposure rate at 1 cm that results from interposition of various thicknesses of lead is shown in Table 2. For example, the use of 0.21 cm of lead will decrease the external radiation exposure by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding

cm of Lead (Pb)	Coefficient of Attenuation
0.0006	0.5
0.015	10^{-1}
0.098	10^{-2}
0.21	10^{-3}
0.33	10^{-4}

*Includes 10 keV x-rays.

To correct for physical decay of the radionuclide, the fractions that remain at selected intervals after calibration time are shown in Table 3.

Table 3. Thallium Tl 201 Decay Chart; Half-Life 73.1 Hours

Hours	Fraction Remaining		Hours	Fraction Remaining
0*	1.00		66	0.53
6	0.94		72	0.51
12	0.89		78	0.48
18	0.84		84	0.45
24	0.80		90	0.43
30	0.75		96	0.40
36	0.71		108	0.36
42	0.67		120	0.32
48	0.63		132	0.29
54	0.60		144	0.26
60	0.57			

* Calibration Time

CLINICAL PHARMACOLOGY

Thallous Chloride Tl 201 with no carrier added has been found to accumulate in viable myocardium in a manner analogous to that of potassium. Experiments in human volunteers using labeled microspheres have shown that the myocardial distribution of Thallous Chloride Tl 201 correlates well with regional perfusion.

In clinical studies, Thallous Chloride Tl 201 images have been found to visualize areas of infarction as "cold" or nonlabeled regions which are confirmed by electrocardiographic and enzyme changes. When the "cold" or nonlabeled regions comprise a substantial portion of the left ventricle, the prognosis for survival is unfavorable. Regions of transient myocardial ischemia corresponding to areas perfused by coronary arteries with partial stenoses have been visualized when Thallous Chloride Tl 201 was administered in conjunction with an exercise stress test. Anatomic configurations may interfere with visualization of the right coronary artery.

After intravenous administration, Thallous Chloride Tl 201 clears rapidly from the blood with maximal concentration by normal myocardium occurring at about 10 minutes. It will, in addition, localize in parathyroid adenomas; it is not specific since it will localize to a lesser extent in sites of parathyroid hyperplasia and other abnormal tissues such as thyroid adenoma, neoplasia (e.g., parathyroid carcinoma) and sarcoid. Biodistribution is generally proportional to organ blood flow at the time of injection. Blood clearance of Thallous Chloride Tl 201 is primarily by the myocardium, thyroid, liver, kidneys and stomach with the remainder distributing fairly uniformly throughout the body. The dosimetry data in Table 4 reflect this distribution pattern and are based on a biological half-life of 2.4 days. Thallous Chloride Tl 201 is excreted slowly and to an equal extent in both feces and urine.

Five minutes after intravenous administration only 5 to 8 percent of injected activity remained in the blood. A biexponential disappearance curve was obtained, with 91.5 percent of the blood radioactivity disappearing with a half-time of about 5 minutes. The remainder had a half-time of about 40 hours.

Approximately 4 to 8 percent of the injected dose was excreted in the urine in the first 24 hours. The whole body disappearance half-time was 9.8 ± 2.5 days. Kidney concentration was found to be about 3 percent of the injected activity and the testicular content was 0.15 percent. Net thyroid activity was determined to be only 0.2 percent of the injected dose, and the activity disappeared in 24 hours. From anterior and posterior whole-body scans, it was determined that about 45 percent of the injected dose was in the large intestines and contiguous structures (liver, kidneys, abdominal musculature).[2]

[2]Atkins, H. L., et al. Thallium-201 for Medical Use. Part 3: Human Distribution and Physical Imaging Properties. Journal of Nuclear Medicine, 18(2):133-140, Feb. 1977.

INDICATIONS AND USAGE
Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging using either planar or SPECT (Single Photon Emission Computed Tomography) techniques for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the perfusion defect.

Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct to the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Thallous Chloride Tl 201 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 and who cannot exercise adequately.

It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.

Thallous Chloride Tl 201 is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for postsurgical reexamination. Thallous Chloride Tl 201 has not been adequately demonstrated to be effective for the localization of normal parathyroid glands.

CONTRAINDICATIONS
None known.

WARNINGS
When studying patients suspected or known to have myocardial infarction or ischemia, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedures. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

PRECAUTIONS
Data are not available concerning the effect on the quality of Thallous Chloride Tl 201 images of marked alterations in blood glucose, insulin or pH (such as is found in diabetes mellitus). Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the Thallous Chloride Tl 201 may likewise be affected.

General
This drug should not be used after six (6) days from the calibration date, or nine (9) days from date of manufacture, whichever comes first.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper management and to insure minimum radiation exposure to occupational workers.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides.

Carcinogenesis, Mutagenesis,
Impairment of Fertility
No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenic potential or whether this drug affects fertility in males or females.

Pregnancy Category C
Animal reproductive studies have not been conducted with Thallous Chloride Tl 201. It is also not known whether Thallous Chloride TI 201 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thallous Chloride Tl 201 should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, as a general rule nursing should not be undertaken when a patient is administered radioactive material.

Pediatric Use
Safety and effectiveness in pediatric patients below age 18 have not been established.

ADVERSE REACTIONS

Following the administration of Thallous Chloride Tl 201, adverse anaphylactoid reactions have been reported (characterized by cardiovascular, respiratory and cutaneous symptoms), some severe enough to require treatment. Hypotension, pruritus, flushing, and diffuse rash which responds to antihistamines have been reported. Other reported events include itching, nausea/ vomiting, mild diarrhea, tremor, shortness of breath, chills, fever, conjunctivitis, sweating, and blurred vision.

Adverse events, some of which were serious, have also been reported in patients who have undergone thallium pharmacologic stress testing (See WARNING). Please refer to the package inserts of approved pharmacologic stress agents for more detailed information on those adverse reactions.

DOSAGE AND ADMINISTRATION

The recommended adult dose of intravenous Thallous Chloride T1 201 for planar myocardial imaging is 37 to 74 MBq (1-2mCi). The recommended intravenous doses for SPECT myocardial imaging are 74 to 111 MBq (2-3 mCi). The efficacy of a 1.0 mCi dose for SPECT imaging has not been well established.

For the localization of parathyroid hyperactivity, Thallous Chloride Tl 201 may be administered before, with or after a minimal dose of a thyroid imaging agent such as sodium pertechnetate Tc 99m or sodium iodide I 123 to enable thyroid subtraction imaging.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if contents are turbid.

Waterproof gloves should be worn during the handling procedures.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

With a shielded sterile syringe, aseptically withdraw the material for use.

For resting Thallous Chloride Tl 201 studies, imaging should begin 10 to 20 minutes after injection. Myocardial-to-background ratios are improved when patients are injected upright and in the fasting state; the upright position reduces the hepatic and gastric Thallium Tl 201 concentration.

When utilized in conjunction with exercise stress testing, Thallous Chloride Tl 201 should be administered at the inception of a period of maximum stress which is sustained for approximately 30 seconds after injection. Imaging should begin within ten minutes after administration to obtain maximum target-to-background ratios. Several investigators have reported that within two hours after the completion of stress testing the target-to-background ratios may decrease significantly in lesions that are attributable to transient ischemia.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[3] at calibration time to an average patient (70 kg) from an intravenous injection of Thallous Chloride Tl 201 are shown in Table 4.

Table 4. Radiation Dose Estimates for Tl 201 Chloride (plus contaminants)

	Estimated Radiation Dose	
Organ	mGy/MBq	rad/mCi
Adrenals	6.2E-02	2.3E-01
Brain	5.9E-02	2.2E-01
Breasts	3.6E-02	1.3E-01
GB Wall	8.3E-02	3.1E-01
LLI Wall	3.4E-01	1.2E+00
Small Intestine	4.5E-01	1.7E+00
Stomach	1.9E-01	6.9E-01
ULI Wall	3.3E-01	1.2E+00
Heart Wall	2.8E-01	1.0E+00
Kidneys	4.6E-01	1.7E+00
Liver	9.9E-02	3.7E-01
Lungs	4.7E-02	1.7E-01
Muscle	4.6E-02	1.7E-01
Ovaries	1.0E-01	3.7E-01
Pancreas	7.4E-02	2.7E-01
Red Marrow	5.5E-02	2.0E-01
Bone Surfaces	8.8E-02	3.3E-01
Skin	3.3E-01	1.2E-01
Spleen	1.8E-01	6.5E-01
Testes	8.2E-01	3.0E+00
Thymus	4.6E-02	1.7E-01
Thyroid	6.2E-01	2.3E+00
Urinary Bladder Wall	5.2E-02	1.9E-01
Uterus	8.5E-02	3.1E-01
Effective Dose Equivalent	3.6E-01/ mSv/MBq	1.3E+00 rem/mCi

Based on data gathered in humans by Krahwinkel et al. (J Nucl Med 29 (9):1582-1586, 1988) and data gathered in humans by Gupta et al (Int J Nucl Med & Biol 8:211-213, 1981).

[3]Values listed include an average maximum correction of 6 percent to the radiation doses from Thallium Tl 201 due to the radiocontaminants Thallium Tl 200 and Thallium Tl 202 on calibration date.

Table 5. Assumed Distribution and Retention

Brain	1.76% $T_{b=\infty}$	
LLI	3.6% T_b=191 hr	(Activity in Wall)
Small Intestine	14.4% T_b=191 hr	(Activity in Wall)
Stomach	2.8% T_b=205 hr	(Activity in Wall)
ULI	4.7% T_b=191 hr	(Activity in Wall)
Heart Wall	3.4% T_b=179 hr	
Kidneys	4.5% T_b=260 hr	0.97% T_b=27 hr
Liver	4.6% T_b=218 hr	
Spleen	0.74% T_b=640 hr	0.28% T_b=37 hr
Testes	1.0% $T_b=\infty$	
Thyroid	0.29% T_b=350 hr	0.24% T_b=166 hr
Total Body	31% T_b=146 hr	69% T_b=502 hr
Urinary Bladder	6.2% T_b=146 hr	13.8% T_b=502 hr
Clearance		

Bladder voiding interval 4.8 hr. Contaminants assumed: Tl 200 (1%), Tl 202 (0.33%), Pb 201 (.33%), Pb 203 (0.33%). Includes dose from Tl 201 Auger electrons. Estimate calculated using phantom of Cristy & Eckerman (Report ORNL/TM-8381/V1 & V7)
Radiation Internal Dose Information Center

HOW SUPPLIED

Catalog Number 120: NDC No. 0019-N120-22, NDC No. 0019-N120-28, NDC No. 0019-N120-56, NDC No. 0019-N120-63, NDC No. 0019-N120-99.

Thallous Chloride Tl 201 is supplied in a sterile, non-pyrogenic solution for intravenous administration. Each mL contains 37 MBq (1 mCi) Thallous Chloride Tl 201 at calibration time, 9 mg sodium chloride and 0.9 percent (v/v) benzyl alcohol. The pH is adjusted to between 4.5 to 7.0 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 81.4, 103.6, 207.2, 233.1, 366.3 megabecquerels (2.2, 2.8, 5.6, 6.3 and 9.9 millicuries) of thallium Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

STORAGE CONDITIONS
Store this drug at controlled room temperature, 20-25°C (68-77°F) [see USP].

Storage and disposal of Thallous Chloride Tl 201 Injection should be controlled in a manner that is in compliance with the appropriate regulations of the government agency authorized to license the use of this radionuclide.

Revised 3/2004
Mallinckrodt Inc.
St. Louis, MO 63134

MALLINCKRODT

A120I0

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7/23/04 03:45:02 PM
Signing for G. Mills

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

NDA# **18-150**
Supplement # SE1-019

Date of letter: 9/29/2003
Due Date: July 30, 2004
Review completed: July 23, 2004

Drug trade name: Thallous Chloride 201 Injection
Active ingredient: Radioactive Thallous Chloride
Chemical name: $^{201}TlCl$

Sponsor: Tyco Health Care
Malincrodt, Inc.
875 McConnel Boulevard
P.O. Box 5840
St. Louis, MO 62134

Pharmacologic Category: Diagnostic Radiopharmaceutical

Proposed Additional New Indication: "Thallous Chloride (^{201}Tl) 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."

Dosage Form(s), Route(s) of Administration and Directions for Use: 1 mCi/mL up to 3 mCi (no carrier added) for planar or SPECT imaging, intravenously.

NDA Drug Classification: Radiopharmaceuticals

Related Drugs: Cardiolite, Cardiotec, Myoview

Executive Summary

1. RECOMMENDATIONS

1.1. Recommendations on Approvability

This NDA supplement should be approved for the same indication currently used for IV Persantine and Adenoscan. At this time, the new portion of indication for Thallous Chloride should include a limitation for use in patients who can not exercise adequately.

1.2 Recommendations on Phase 4 Studies and Recommendations on Postmarketing Studies and/or Risk Management Steps

No new post-marketing studies and/or risk management steps are needed at this time provided that all the safety sections currently in the package inserts for IV Persantine and Adenoscan will be copied into the new labeling for rest/stress Thallous Chloride, or an appropriate reference to those drugs' labels will be made. In the future, if the sponsor opts to remove some of these precautions and/or limitations from the labeling, additional relevant safety data should support the change.

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Scope of the submission: This submission contains 4 volumes including an introductory letter requesting a new indication for rest and stress imaging of myocardial perfusion following pharmacologic stress.

The Summary Basis of Approval for IV Persantine (NDA #19-817) and Summary Basis of Approval for Adenoscan (NDA #20-059) form the more substantive portion of this application. Those were supplemented in this submission by a collection of copies of medical literature articles on safety and efficacy of both drugs, when used during scintigraphic imaging in conjunction with Thallous Chloride. Additional literature articles describe a framework and potential basis for the submission of literature articles in lieu of Phase 3 study results.

The clinical literature articles expressed a variety of experiences with, and opinions on rest and stress imaging. The investigators used pharmacologic agents for stress along with Thallous Chloride with different imaging methodologies, equipment, data processing, patient populations, etc. The potential scope of Thallous Chloride imaging along with pharmacologic agents in the target population was well covered, but the imaging performance criteria in subjects without an obvious disease were addressed less well.

Mechanisms of action: Thallium is a heavy metal and may be toxic except in negligible concentrations such as is the case for myocardial perfusion imaging. It acts non-specifially throughout the myocardium marking the available blood flow in a way reminiscent to potassium.

Adenosine and dipyridamole act both along the same cellular pathway causing coronary vasodilation. Exogenous adenosine adds to the endogenous adenosine to increase total available adenosine concentration, while dipyridamole acts indirectly by blocking the endogenous adenosine uptake. Dipyridamole may also prevent inactivation of adenosine by red blood cells. Consequently, the action of adenosine used for pharmacologic stress is faster and more direct, while that of dipyridamole's is slower and, perhaps, less optimal and less conducive to titration in regard to optimal stress and/or imaging. Tri-exponential decline in plasma levels is characterized by the 3-12 minutes, 33-66 minutes and 11.6 -15 hours half lives, respectively.

Theophylline competitively antagonizes the action of adenosine, and aminophylline has been shown clinically to treat adverse events related to Adenoscan administration.

2.2. Efficacy

The efficacy of Thallous Chloride pharmacologic stress test with either IV Persantine (NDA #19-817) or Adenoscan (NDA #20-059) has been established by the Agency's prior decision (please see medical team leader's review for detailed information) and consulted with Cardio-renal Division HFD-110 that was the primary review division. A review of a meta-analysis of all relevant thallium pharmacologic stress studies between 1982 and 2002 showed a higher estimates on sensitivity and specificity of thallium pharmcologic stress test, compared to that in the original clinical trials used to support the Agency's prior approval. In the opinion of this reviewer, the results support the performance of thallium pharmacologic stress test in terms of sensitivity and specificity.

2.3. Safety

No additional safety analysis is conducted. All safety information in current IV Persantine or Adenoscan should be stated in thallium product label, or appropriately referred to.

2.4. Dosing. Regimen and Administration

The sponsor proposed no changes in dosing and administration of Thallous Chloride (^{201}TlCl).

2.5 Drug-Drug Interactions

The subject of drug-drug interaction has not been specifically addressed in this submission.

2.6 Special Populations

No special populations have been specifically addressed in this submission.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug. Drug Class. Sponsor's Proposed Indications(s), Dose, Regimens, Age Groups

The established name for the imaging drug is thallous chloride and its trade name is Thallous Chloride ^{201}TlCl Injection. No name changes were proposed in this submission. It is a carrier-free diagnostic radiopharmaceutical. The name of the pharmacologic stress agents considered in the new indication are dipyridamole, trade name IV Persantine and adenosine, trade name Adenoscan. These are currently approved for scintigraphic pharm stress imaging.

The proposed new addition to the current efficacy portion of the indication, if approved, would read as follows: Thallous Chloride ^{201}Tl 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.

No changes in the current dosage and administration such as of the label are proposed.

1.2 State of Armamentarium for Indication

As already mentioned, two pharmacologic agents are currently approved for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress in patients with known, or suspected coronary artery disease. These are IV Persantine and Adenoscan. Their respective indications read as follows:

" Persantine IV is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately."

"Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately."

1.3 Important Milestones in Product Development

Thallous Chloride was approved for cardiac imaging including at stress in 1985. IV Persantine and Adenoscan were approved for pharmacologically induced cardiac stress thallium imaging in patients who can not exercise adequately in 1990 and 1995, respectively.

1.4 Other Relevant Information

None

1.5 Important Issues with Pharmacologically Related Agents

Thallium is a heavy metal and may be toxic except in negligible concentrations such as is the case for myocardial perfusion imaging. It acts non-specifially throughout the myocardium marking the available blood flow. Its effect on myocardium is believed to be similar to that of potassium.

Dipyridamole acts indirectly by blocking the endogenous adenosine uptake. Dipyridamole may also affect metabolism of adenosine by platelets. When compared with each other, the action of adenosine used for pharmacologic stress is faster and more direct, while that of dipyridamole slower and, perhaps, less optimal and less conducive to titration in regard to optimal stress and/or imaging.

2 SIGNIFICANT FINDINGS FROM CHEMISTRY, CLINICAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS AND/OR MICROBIOLOGY

No pre-clinical reviews have been conducted for this new indication.

3. PHARMACOKINETICS AND PHARMACODYNAMICS

3.1 Pharmacokinetics

No biopharmaceutics reviews have been conducted for the new indication.

3.2 Pharmacodynamics

No biopharmaceutics reviews have been conducted for the new indication.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

Through the Freedom of Information, the sponsor obtained summary information for IV Persantine NDA and Adenoscan NDA. The sponsor also conducted a meta-analysis from 25 clinical studies involving those pharmacologic stress agents and thallium. Published articles were provided but the sponsor obtained no right of reference to those data.

4.2 Overview of Clinical Trials

None

4.3 Postmarketing Experience

No additional analyses were conducted.

4.4 Literature Review

Fifteen literature articles on persantine iv stress imaging from peer-reviewed journals were submitted in support of the new indication. These papers were published between 1982 and 1999, with about a half available in 1990, therefore, before the original Persantine IV approval. Two of the submitted articles were selected and are summarized in Appendices A and B to illustrate the nature of the articles submitted by the sponsor and the scope of the information obtained therewith.

Ten literature articles on adenosine imaging from peer-reviewed journals were submitted in support of this new indication. These papers were published between 1991 and 1997, with the majority available in 1994, therefore before the original Adenoscan approval. Two of the submitted articles were selected and are summarized in Appendices C and D to illustrate the

nature of the investigations submitted and the scope of the information considered by the sponsor.

Those articles described various aspects of the clinical use of Persantine IV or Adenoscan in conjunction with Thallium imaging in different patient groups and using various imaging techniques and equipment. Heterogeneity in patient population, imaging techniques and equipment precludes rigorous statistical evaluation and restricts general applicability of the conclusions from any individual article to the cardiac patient population as a whole. Thus, the article collection may serve as examples on clinical utility of the methodology in specific patient populations, using different imaging equipment and procedures including qualitative and quantitative methods.

5. CLINICAL REVIEW METHODS

5.1 General Approach

The objective of this review is to ensure that results from meta-analysis of relevant pharmcologies stress studies cast no doubt on the performance of the ^{201}TlCl test in terms of sensitivity and specificity as well as safety

5.2 Overview of Materials Consulted in Review

All published articles that describe studies included in the meta-analysis were reviewed and two of the key studies for each pharmacologic agent, IV Persantine and Adenoscan, were reviewed in a great detail (Appendices A, B and C, D, respectively.)

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI inspection was conducted and all literature information was not verified independently.

5.4 Were trials Conducted in Concordance with Accepted Ethical Standards

Most of the trials described in the literature articles were done in academic institutions and with the approval of an IRB.

5.5 Evaluation of Financial Disclosure

A financial disclosure statement was not submitted.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Brief Statement of Conclusions

The data presented from meta-analysis cannot be used as the key evidence to support the efficacy of thallium pharmacologic stress agent because of the heterogeneity in patient population, imaging techniques and equipment. However, the meta-analysis results despite serious

limitations showed mostly acceptable sensitivity and specificity when IV persantine or adenosine was used in conjunction with Thallium imaging.

6.2 General Approach to Review of the Efficacy of the Drug

As stated earlier, the objective of reviewing the meta-analysis conducted by the sponsor is NOT to demonstrate the efficacy but rather to examine whether more recent data cast any doubt on the performance of thallium pharmacologic stress test in terms of sensitivity and specificity.

6.3 Detailed review of Trials Indication

The currently approved indication for IV Persantine reads as follows :" Persantine IV is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately."

Similar approved indication for Adenoscan reads as follows :"Intravenous Adenoscan is indicated as an adjunct to ^{201}Tl myocardial perfusion scintigraphy in patients unable to exercise adequately."

It transpires that the efficacy issues related to the general pharmacologic claim, in conjunction with Thallous Chloride imaging for Persantine or Adensocan, can not be addressed in this review in detail because of lack of necessary relevant exercise data, and the lack of supportive background data in original NDA review.

That being said, this reviewer examined 25 studies that were included in the meta-analysis. It appears that all studies met the following criteria:

- All patients were with known or suspected coronary artery disease
- All patients had both thallium imaging stress test and coronary angiography
- All tests were read blindly
- Sensitivity and specificity were the endpoints of the study

1,217 patients (from 14 studies) received IV Persantine, and 1,397 patients received Adenoscan. Sensitivity and specificity of thallium imaging were calculated separately for two pharmacologic stress agents. Two study subgroups were established for each stress agent based on the severity of coronary stenosis as determined by angiography luminal area narrowing either $\geq$ 50% or $\geq$ 70%.

The meta-analysis showed that the sensitivity of thallium pharmacologic stress test is between 89% and 93% regardless of pharmacologic agents used or criteria used to define coronary artery disease (i.e., 50% or 70% stenosis). The lower limit of 95% CI was approximately 85%. The estimates of specificity, however, varied significantly (from 64% to 100%). While the specificity estimates are not as stable as that of the sensitivity, they are, in general, higher than that from the original clinical trials of each pharmacologic stress agent (please see statistical review for detailed meta-analysis results).

This reviewer examined all 25 studies individually. Table 1 listed the performance of each study, type of pharmacologic stress agent, criteria for defining coronary artery disease, and number of subjects in each study. The sensitivity from each study ranged from 79% to 96%, and specificity from 47% to 100%.

Table 1. Literature articles submitted in support of the proposed indication for Thallous Chloride (Vol. 2, p 2.100 - 2.376)

Reference	Authors	Year of publication	Dipyridamole	Adenosine	Prospective study	Consecutive patients	Blinded read	Patient number		Coronary angiography cut-off (%)		Sensitivity	Specificity	Notes
								Efficacy	Safety					
12	Norris et al.	93	x					32			*70*	95	56	
13	Kong et al.	92	x					114	114	50		87	58	*Men vs women*
14	**Mendelsohn et al.**	**92**	**x**					**79**	**-**	**50**	**70**	**89**	**70**	
15	Perin et al.	91	x					25		50		80	85	
16	**Zhu et al**	**91**	**x**			**x**		**170**	**170**		**70**	**91**	**79**	
17	DePuey et al.	89	x					76	356	*50*		89	47	
18	Boudreau et al.	90	x		x			80	-		70	86	72	*Diabetic patients*
19	Huikuri at al.	88	x					93	93		70	96	-	*Hand grip study*
20	Lam et al.	88	x					142	337		70	83	70	*Elderly*
21	Taillefer at al.	86	x					50			70	79	86	*Oral vs i.v. administration*
22	Sochor et al.	84	x					194		*not done*		92	81	
23	Okada et. al.	83	x					29	30	*50*		91	100	
24	Francisco et al.	82	x			x		86			70	90	96	*Qualitative vs quantitative evaluation*
25	Leppo et al.	82	x					60	60	*50*		93	80	
27	Taillefer at al.	96	x	x	x			54	54		70	87	-	
26	Patsilinakos at al.	99		x				50	50	50		85	77	*Severe aortic stenosis*
28	Fenster et al.	97		x				13	13			-		
29	Aksut et al.	95		x				443		50		87	70	*Lack of detail on safety*
30	Iskandrian et al.	90		x				59	59	50		94	100	
31	Ogilby et al.	92		x				45	45			94	100	
32	Iskandrian et al.	93		x				339	339	50		90	90	
33	Coyne et al.	91		x				100	100	*50*		83	75	
34	**Nishimura et al.**	**91**		**x**		**x**		**101**	**101**	**50**	**70**	**87**	**90**	
35	Verani et al.	90		x				89	89	*50*		83	94	
36	**Iskandrian et al.**	**91**		**x**				**148**	**148**	*50*		**92**	**88**	
	Total							2,671	2,158					
	Total for dipyridamole							1,284	1,214					
	Total fo adenosine							1,441	998					

This reviewer also identified four studies (two for each pharmacologic stress agent) that appear to be well conducted, at least on paper, with adequate sample size (see Appendix A to D). The sensitivity and specificity are higher than 87% and 70%, respectively.

6.4 Efficacy Conclusions

Although performance of pharmacologic stress agents in conjunction with Thallium imaging in the submitted articles may be higher than that from the original clinical trials as stated in IV Persantine or Adenoscan product label, meta-analysis has many limitations, including the inability of verifying the results independently. The data cannot be used to support the efficacy of Thallous Chloride pharmacologic stress agent. Since the objective of this review is not to demonstrate the efficacy, this reviewer believed that the data can be used to support the statement. i.e., there is little evidence to suggest diminished performance of Thallous Chloride pharmacologic stress test in terms of sensitivity and specificity.

Whether benefit of the imaging procedure in the entire cardiac patient population can outweigh the risk was not addressed sufficiently in the original submission. Therefore pharmacologic stress tests were limited to patients who cannot exercise adequately. Data presented here cannot be used as the evidence of improved performance. As a result, the limitation, in regard to the patients who can not exercise adequately, should not be lifted.

7 INTEGRATED REVIEW OF SAFETY

7.1.Brief Statement of Findings

The Summary Basis of Approval for IV Persantine describes a safety profile for the combined use ^{201}TlCl and Dipyridamole in target population. It was found that there was approximately 0.075 % fatality rate for the imaging test which was about 15 times higher than the observed fatality rate for exercise testing. In addition, there was about 0.4% chance of serious, nonfatal reactions such as myocardial infarction, symptomatic ventricular arrhythmias, transient cerebral ischemia and bronchospasm. The fatality rate was included in the risk benefit analysis and subsequently considered to be the most compelling reason for limiting the use of IV Persantine to patients who can not exercise adequately (in the indication).

Incidence of adverse events described in the publications submitted as part of this supplement does not differ substantially from that reported in the original NDA review for Persantine and from the incidence of drug related adverse events in the current package insert for Persantine IV. However, there was no attempt in the literature reports to categorize the AE by severity.

The Summary Basis of Approval for Adenoscan describes a safety profile for the combined use ^{201}TlCl and adenosine in the target population. Death occurred with a frequency of approximately 5/10,000, and other most prominent adverse events were dyspnea and chest pain. The deaths were included in the risk benefit analysis and subsequently the most compelling reason for limiting the use of Adenoscan to patients who can not exercise in the indication.

Incidence of adverse events described in the literature articles submitted as part of this supplement does not differ substantially from that reported in the original NDA review for Adenoscan. However, there was no attempt in the literature reports to categorize the AE by severity.

7.2.Materials Utilized in Review

This brief safety review was limited to information provided as a part of the Summary Basis of Approval of Persantine IV supplemented by a survey of adverse events reported in 8 literature articles submitted by the sponsor and summarized in Table 2. Similar Summary Basis of Approval of Adenoscan was supplemented in this submission by a survey of adverse events from 7 literature articles summarized in Table 3.

7.3.Description of Patient Exposure

The initial NDA submission for dipyridamole contained data collected by the sponsor and carried out by 64 investigators in 1,096 patients with additional published reports on 2,406 patients.

The literature articles submitted by the sponsor in this supplement report on adverse events in 1173 patients.

For adenosine, the initial NDA submission contained data on 1,067 consecutive patients with the safety observation period extended to 24 hours, and 5,552 patients observed for safety only during the immediate time of actual testing.

The literature articles submitted by the sponsor in this supplement related to adenosine report on adverse events in 1093 patients.

7.4.Safety Findings from Clinical Studies

Please see IV Persantine and Adenoscan product label for more information (Please see Medical Team Leader's Review).

7.5.Miscellaneous Studies

N/A

7.6.Literature Review for Safety

The literature articles on persantine did not categorize adverse events by severity. Six of seven deaths reported, which occurred within a 6-month follow-up period, were found to be coronary-related. Among them were two patients who died after coronary bypass surgery, three patients

determined inoperable and who subsequently died from episodes related to ischemia and/or heart failure, one patient who died after vascular surgery, and one patient who had complications of severe chronic pulmonary disease. Thus, a clear-cut association between the imaging procedure and those deaths was not established.

As shown in Table 2, chest pain was the most frequent adverse event followed by headache and dizziness. There was a considerable variability in incidence of adverse events among different investigators likely due to different patient population, length of follow-up, patient treatment, etc.

Table 2. Adverse events related to thallous chloride rest and stress imaging using dipyridamole *

Reference number	**13****	**15**	**16**	**17**	**19**	**20**	**23**	**25**	**26**
Sample size (N)	**114**	**25**	**170**	**356**	**81**	**337**	**30**	**60**	**50**
Deaths			7						
Cardiac									
Chest pain	37%; 25%		44%	12%	12%	25%	27%	18%	42%
ECG changes	33%; 16%		10%	3%		8%		12%	
Severe Ischemia	9%; 1%					2%			
Dyspnea			3%		3%				36%
Noncardiac									
Dizziness	12%; 1%	4%	13%	8%	9%	5%		15%	36%
Headache	19%; 8%	28%	19%	18%	5%	11%		20%	20%
Nausea	7%; 6%	4%	9%	7%	4%	3%		10%	10%
Flushing	0%; 7%	4%		1%		2%			46%
Hypotension		4%							
Epigastric discomfort			2%						
Arm pain				1%					

*References where the adverse events were not clearly categorized and quantitated are not listed.
** The first number (%) refers to adverse events in women and the second in men.

In regard to adenosine, as shown in Table 3, chest pain, flushing and dyspnea were the most frequent adverse events followed by headache and dizziness. There was a considerable variability in incidence of adverse events among different investigators likely due to different demographics, length of follow-up, patient treatment, etc.

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Table 3. Adverse events related to thallous chloride rest and stress imaging using adenosine*

Reference number	26	31	32	33	34	35	36
Sample size (N)	**50**	**45**	**559**	**100**	**101**	**89**	**149**
Cardiac							
Death							
Chest pain	42%	80%	52%	57%	40%	57%	48%
ECG changes	21%			3%		12%	
Severe Ischemia						2%	
Dyspnea	36%	24%	51%	62%	19%	15%	
ST depression > 1mm		27%	24%				48%
1st degree or higher AV block		9%	4%	4%	2%		3%
Hypotension		2%					
PR prolongation					15%		
Noncardiac							
Dizziness	36%	4%	8%	7%	18%	5%	7%
Headache	20%	16%	15%	22%		35%	1%
Nausea	10%		12%	24%	5%	3%	9%
Flushing	46%	44%	55%	61%	26%	29%	61%
Epigastric discomfort		4%	9%				5%
Arm or leg pain				14%			
Throat tightness				32%	8%		
Jaw pain					2%		

*References where the adverse events were not clearly categorized and quantitated are not listed

7.7.Postmarketing Surveillance If Applicable

None

7.8.Safety Update If Available.

None

7.9 Drug Withdrawal. Abuse, and Overdose Experience

N/A

7.10 Adequacy of Safety Testing

The original NDA safety review for Persantine IV evaluated 3,911 patients from various trials under physician-sponsored INDs for dipyridamole. The literature articles submitted as a part of this supplement described adverse events in 1,173 patients, but some of these might have been already included been reported on among those 3,911 patients mentioned earlier.

The original NDA safety review for Adenoscan evaluated 1,067 consecutive patients with the safety observation period extended to 24 hours, and 5,552 patients, observed for safety, only during the immediate time of actual testing. The literature articles submitted by the sponsor in this supplement report on adverse events in 1093 patients. Some of these could have been evaluated for the original NDA review. The patient populations appear sufficiently representative of target population.

Limitations of this database include: a) availability of only adverse event reporting, without commenting on other potential safety related changes such as vital signs; b) lack of classification of adverse events (severe, moderate, mild) and c) great heterogeneity of data because of the patient population, technology, patient treatment, etc. Despite those limitation, no additional safety study is recommended.

7.11 Labeling Safety Issues and Postmarketing Commitments

The following statement should be included under WARNING section of thallium Thallous Chloride product label:

- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

8. DOSING, REGIMEN AND ADMINISTRATION ISSUES

No dose change was proposed in this submission for ^{201}TlCl. The currently approved dose for SPECT imaging with Thallium is up to 3 mCi (no carrier added).

9. USE IN SPECIAL POPULATIONS

Use of Thallous Chloride pharmacologic stress test should only be limited to patients who cannot exercise adequately.

Reviewed by:

Joseph Zolman, MD
Medical Officer

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Appendix A

Article title:	Usefulness of Single-Photon Emission Computed Tomography of ^{201}Tl Uptake After Dipyridamole Infusion for Detection of Coronary Artery Disease
Authors:	Maria A. Mendelson, MD, Stewart M. Spies, MD, William G. Spies, MD, Pierre Abi-Mansour, MD, Dan J. Fintel, MD
Journal and year of publication:	Am J Cardiol 1992; 69: 1150-1155
Investigative site:	Northwesterm University, Chicago, Ill, USA
Objective:	To compare the diagnostic performance of SPECT and and planar ^{201}Tl imaging for the overall detection of CAD in individual vascular territories.
Number of patients:	79
Demographics:	Patients had a mean age of 60 ± 11.1 years (range 33 to 83) And 73% were men. There was evidence of CAD in 96% of the patients: 70% (55) had a prior myocardial infarct and
75%	had at least 1 artery with a lumen diameter narrowing of ≥70%. The distribution of CAD in the individual vascular territories was nearly identical for men and women. There were 18 patients who had either noncritical coronary disease, or a patent vessel but had a wall motion abnormality and a history of myocardial infarction. Of these, 4 had 50 to 69% stenosis in at least 1 vessel and the remainder had <49% stenosis.
Inclusion criteria:	Patients with known or suspected CAD underwent dipyridamole ^{201}Tl scintigraphy within a mean of 14 days of cardiac catheterization from the period of September 1985 through May 1988. The decision for cardiac catheterization was the patient's attending physician for clinical indication.
Exclusion criteria:	Patients with unstable angina or severe bronchospastic
disease	receiving aminophylline.
Dose:	Dipyridamole, 0.56 mg/kg, was infused over 4 minutes through a Harvard infusion pump under the supervision of

a cardiologist.

Three mCi (111 MBq) of ^{201}Tlwere administered
4 minutes after the completion of dipyridamole infusion.

Imaging and data acquisition: Planar ^{201}Tl imaging was performed using a gamma camera equipped with a low-energy, all-purpose parallel hole collimator. Each image was acquired for 5 minutes and consisted of approximately 750,000 counts. Following planar imaging, SPECT acquisition was performed over a 180^0 arc from the right anterior oblique to the left posterior oblique projection using a noncircular orbit with 64 angular samples obtained at 20 seconds per projection. Images were reconstructed using a filtered back-projection algorithm. Tomographic data were presented in horizontal long-axis, vertical long-axis and short-axis slices. The images were recorded on 8 X 10 inch x-ray film. Redistribution images were acquired 3 hours later using the same protocol.

Cardiac catheterization was performed after an overnight fast using either standard Judkins or Sones technique. Coronary angiography was obtained in multiple orthogonal projections and single or biplane left ventriculograms were performed.

Blinded read: Immediate and delayed ^{201}Tl planar images were interpreted by experienced observers unaware of patient identity, and clinical and angiographic findings. Paired SPECT images were assessed in the same manner at a different reading session. Differences were resolved by consensus. The severity of disease was assessed using a 5 point scale: (1) definitely normal, (2) probably normal, (3) equivocal, (4) probably abnormal, and (5) definitely abnormal. An abnormal study was defined as either 4 or 5 ("strict" criteria) or with the addition of equivocal scans 3, 4 or *5* ("liberal criteria"). For the purpose of scintigraphic analysis vascular territories were divided into the anterior circulation, the myocardium supplied by the left anterior descending artery, and the posterior circulation supplied by the right and left circumflex coronary arteries.

Cineangiograms were evaluated by an experienced angiographer unaware of both clinical and scintigrapbic data. Vessel diameter stenosis was estimated visually using a 5 point scale: (0) normal, (1) 0 to 49% stenosis, (2) 50 to 69% stenosis, (3) 70 to 99% stenosis, and (4) 100% artery occlusion. The severity of wall motion abnormalities was assessed using a 4 point scale: (1) normal, (2) hypokinetic, (3) akinetic, and (4) dyskinetic. CAD was defined as a stenosis of ≥70% lumen diameter narrowing or a wall motion abnormality and a history of a myocardial infarction. Mild stenosis was defined as a vessel narrowing of 50 to 69%. Extent of CAD was defined as the number of vessels with stenosis of ≥70%. Myocardial infarction was defined by clinical history or electrocardiographic evidence of a myocardial infarction.

Statistics: Patients were excluded from analysis if myocardial infarction, coronary revascularization, or if clinical deterioration had occurred between the time of dipyridamole ^{201}Tl testing and cardiac catheterization.

Categorical data comparisons of sensitivities were made by chi-square analysis. Specificity could not be assessed for overall detection of CAD because of the high prevalence of CAD in the study population. Specificity could be determined for individual vascular territories. Statistical differences between receiver-operating characteristic curves employed the area test. Differences were considered significant at $p < 0.05$.

RESULTS

Sensitivity

Using strict criteria, an abnormal scintigraphic study was defined as definitely or probably abnormal. The overall detection of CAD by SPECT was 89% compared with 67% by planar scans ($p < 0.01$). When the detection of CAD was evaluated for the individual vascular territories, the detection of disease in the anterior vascular territory (left anterior ascending artery) by SPECT was 69% compared with 44% by planar scans ($p < 0.01$).

It was thought to be a useful clinical designation to assess the right coronary and left circumflex arteries as a combined posterior vascular territory since the patients studied had both right and left dominant coronary artery circulations. In the posterior circulation SPECT had a sensitivity of 80% compared with 54% by planar study ($p < 0.01$). When the comparison was performed with more liberal ("3—5") criteria, planar scanning in the anterior vascular territories had a sensitivity of 73% for detection of a defect compared with 86% with SPECT ($p < 0.01$). In the posterior vascular territory, when the liberal enteia were used, planar and SPECT had similar sensitivities of 81% and 87%, respectively. Therefore, when planar scans were read incorporating "equivocal" studies as abnormal or positive, the sensitivity for detection of CAD approached that of SPECT at a strict decision threshold.

Specificity

Specificity in individual vascular territories improved when strict criteria were used. This improvement was significant for planar scans. Specificity for SPECT was significantly higher for anterior vascular territory only using liberal criteria, but it was significantly lower than in planar imaging for the posterior vascular territory. Overall specificity for SPECT also decreased in the posterior vascular territory.

Receiver-operating characteristic analysis

Diagnostic accuracy for detection of disease in the anterior and posterior vascular territories was evaluated by generating receiver-operating characteristic curves. Each operating point represented the sensitivity/specificity pair generated at a particular decision threshold. For anterior circulation, SPECT demonstrated improved diagnostic performance at multiple decision thresholds compared with planar scintigraphy. At most decision thresholds for the posterior circulation, SPECT achieved higher sensitivity but lower specificity than planar imaging. The nearly superimposable receiver-operating characteristic curves demonstrated similar diagnostic performance. This pattern was similar to that previously described with exercise thallium tomography. Receiver-operating characteristic analysis could not be performed for the overall detection of CAD because of the small number of patients without CAD in the study cohort. For

this reason, receiver-operating characteristic curves could also not be generated for the subset analyses of the nature and extent of CAD as well as the presence of prior myocardial infarction.

Effect of prior myocardial infarction on ^{201}Tl scintigraphy results

A history of a prior myocardial infarction was present in 55 patients (70%). SPECT had significantly improved sensitivity in the presence of a myocardial infarct compared with planar scintigraphy: 93 vs 75% ($p < 0.01$). Even in the absence of a prior myocardial infarction, SPECT had an improved sensitivity for detection of disease of 81% compared with 50% for planar imaging ($p < 0.05$).

Effect of severity of coronary artery stenosis on ^{201}Tl scintigraphy results

Angiographically critical disease defined as ≥70% luminal narrowing of at least 1 artery was found in 59 patients (75%). In these patients, SPECT had significantly improved disease detection 90% compared with 69% for planar imaging ($p \leq 0.01$). As CAD is a diffuse process, there may be clinically significant disease of ≤50 to 69% stenosis, which may not be considered angiographically critical. Coronary artery narrowing of lesser degrees was found in only 12 patients (15%), in whom detection of disease was 83% for SPECT and 58% for planar imaging. This difference did not achieve statistical significance because of the small sample group size.

Extent of coronary artery disease on ^{201}Tl scintigraphy results

In the 33 patients with stenosis in only 1 coronary artery, CAD was detected with 88% sensitivity by SPECT compared with 58% by planar imaging ($p \leq 0.01$). In the 43 patients with significant luminal stenoses in >1 coronary artery, SPECT had improved sensitivity of 91% compared with planar sensitivity of 74% ($p \leq 0.05$).

Appendix B

Article title: Tomographic ^{201}Tl Myocardial Perfusion Scintigrams After Maximal Coronary Artery Vasodilation with Intravenous Dipyridamole: Comparison of Qualitative and Quantitative Approaches

Authors: Dan Francisco, Steven M Collins, Raymond Go, James Ehrhardt, Owen C Van Kirk and Melvin Marcus

Journal and year of publication: Circulation 66, No. 2, 1982

Investigative site: University of Iowa, Iowa City, Iowa, USA

Objectives: To test several quantitative approaches to determining the lower limit of the normal ^{201}Tl distribution and to determine whether moderate coronary obstructions are associated with ^{201}Tl perfusion defects.

To determine the combined effects of three approaches (quantitative image analysis, coronary dilatation with dipyridamole and tomographic scintigrams) on the sensitivity and specificity of detecting significant CAD with ^{201}Tl scintigraphy.

Number of patients: 86

Demographics: There was no reference to patient demographics except for a history of cardiac disease and concomittant medications as follows: The precatheterization diagnosis in the 51 patients shown to have significant CAD ≥70% diameter narrowing) was stable angina in 18, unstable angina in 18, valvular heart disease in 14, and atypical chest pain in one patient. Patients classified as having unstable angina had either one or more prolonged episodes (> 30 minutes) of substernal chest pain unresponsive to nitroglycerin or a 50% increase in the frequency of their angina within 2 months before admission. None of the patients with unstable angina was having frequent episodes of rest pain or required narcotic drugs for pain relief within 3-7 days of the imaging procedure.

The 35 patients with insignificant CAD were divided into a group that had no or minor CAD (<30% diameter narrowing of a coronary artery (24 patients) or moderate CAD (30-55% diameter narrowing or systolic compression of one coronary artery). Twenty of the 24 patients with insignificant CAD had no coronary obstructions and four had one-vessel obstruction (25-30% diameter narrowing in the left anterior descending coronary artery). The clinical diagnosis in those patients was atypical chest pain in 12, unstable angina in eight, and valvular heart disease in four. The clinical diagnosis in 11 patients shown to have moderate CAD were atypical chest pain in three, unstable angina in two and valvular heart disease in six.

Inclusion criteria: Patients scheduled to have a diagnostic cardiac cathetrization

and coronary angiography were studied.

Exclusion criteria: Patients with an acute myocardial infarction in the previous 6 weeks or life-threatening cardiac dysrhythmias, such as recurrent ventricular tachycardia or ventricular fibrillation.

Dose and the route of administration: With the patient in the supine position, dipyridamole was infused through a 21-gauge butterfly needle placed in a forearm vein. A calibrated infusion pump delivered the drug at 0.15 mg/kg/mm for 4 minutes. During the procedure, arterial pressure was recorded with a sphygmomanometer, and a 12-lead ECG recording was obtained each minute. Cardiac rhythm was monitored continuously.

After the dipyridamole infusion was completed, the patient sat up, stood, and then walked in place at a rate of 10-30 steps/min. At this point (30-60 seconds after cessation of the dipyridamole), 1.5 mCi of ^{201}Tl was injected i.v. and the cannula was flushed with 5 ml of saline. The patients continued to walk in place for 4-5 minutes longer. Patients were standing before the ^{201}Tl injection. At lower left atrial pressures, the heart/lung ratio of ^{201}T1 activity is increased, and consequently, image quality improves. At the end of the procedure, the venous cannula was removed and the patient was taken to the nuclear medicine laboratory. The imaging procedure was usually begun within 10-15 minutes from the time of ^{201}Tl injection.

Imaging and data acquisition: Each patient had both a planar (conventional) and tomographic ^{201}Tl myocardial perfusion scintigram. The order of performing these studies was altemated. We used a Searle large-field-of-view gamma camera and a seven-pinhole collimator. The camera was placed in the 40 ° left anterior oblique position and adjusted so that the views covered as much of the crystal face as possible -and the central pinhole image was more annular than the other views. Each seven-pinhole study consisted of two data acquisition images of 350,000 counts each. The energy discriminator was set at 80 keV with a 30% window. These two images were collected over 10-15 minutes.

The planar ^{201}Tl images were obtained with a small-field-of-view gamma camera using a low-energy, parallel-hole, all-purpose collimator. The images were obtained in the anterior, 400 and 600 left anterior oblique and left lateral projections. The energy discriminators were set at 1.64 keV with a 25% window and 74 keV with a 35% window. The total imaging time for the conventional images was 25-40 minutes. No redistribution images were obtained.

Multiple views of the right and left coronary arteries were obtained in all patients using the Judkins technique. Each patient also had a left ventriculogram using either an angiographic or radionuclide approach.

Tomographic Analysis: From each seven-pinhole scintigram and previously acquired calibration images, 12 cross-sectional cardiac images (tomograms) were constructed using a computer system and a previously reported simultaneous multiple-angle reconstruction technique. These

images are formed at approximately 1-cm intervals. The three most central scintigrams of the left ventricle (apical, central and basal) were used for quantitative analysis. A computer program asked the operator to indicate the center of the ventricular cavity in the apical plane. The computer then divided the cardiac image into 60 6 ° "pie segments." The "hottest," or maximal, pixel in each segment is located and displayed to the operator as a contour superimposed on the myocardial image. This program does not use a ray-sampling technique, and thus does not ignore any pixels in the image. If the contour of the hot pixels fell wholly within the myocardium, the operator instructed the computer to plot the magnitude of the hot pixels around the circumference of the heart. If the contour fell partially outside of the myocardium, the radius within which the program searches for the maximal pixel was shortened until the contour fell wholly within the myocardium. The curve was normalized by expressing each point as a percentage of the hottest pixel in the image. The above procedure was repeated for the central and basal planes.

Starting at the 3 o'clock position and proceeding clockwise, the left anterior descending coronary artery distribution corresponds to 0-270° in the apical plane and 100° -270° in the central and basal planes of the tomogram. The left circumflex artery distribution was taken to correspond to 270°-360° in all three planes, while the right coronary artery corresponded to 0-100° in the central and basal planes.

In each patient, three curves (apical, central and basal) derived as described above were used for quantitative analysis of the tomograms.

Lower Limit of Normal Curves: The "lower limit of normal" curve defined the normalized ^{201}Tl activity below which a patient's perfusion distribution curve must fall in order to be considered abnormal. If the patient's perfusion curve crossed below the lower limit or normal curve in any one of the three planes, the patient was considered to have a perfusion defect and the tomogram was positive.

Mean curves in each of three planes were derived from the patients with normal coronary arteries by averaging their individual curves point by point. One patient's data were excluded from normal distribution because she was an obvious false positive. In determining the specificity of our imaging procedure, however, this patient was included. A set of lower limit of normal curves was derived by subtracting a variable number (1.0-4.0) of standard deviations (also calculated on a point-by-point basis) from the mean curve.

An alternative approach for defining the lower limit of normal is to use the range. Such a range curve was calculated by finding the minimum value (point by point) of the curves from patients with norma] coronary arteries.

Moderate CAD: To assess the effect of including patients with moderate CAD on the definition of the normal curve, a range curve was calculated from all patients without significant CAD, i.e., normal subjects and patients with moderate CAD.

A scintigram was considered abnormal if the patient's values dropped below the normal range at one or more points. The location of a coronary lesion was said to be concordant with the perfusion defect on the tomogram if the patient's perfusion curve fell below the lower limit of normal at one or more points in the distribution of the obstructed coronary artery.

Blinded read: The planar and tomographic ^{201}Tl scintigrams were analyzed visually by three experienced observers who did not know the names of the patients, results of the cardiac catheterizations or clinical history. An abnormality was defined as a discrete region of absent or decreased ^{201}Tl activity. The scintigrams were graded as normal or abnormal. Disagreements in interpretation were resolved by consensus. During the initial reading, if the interpretation of the various observers differed (abnormal vs normal), this was recorded as an instance of interobserver variability.

Analysis of the coronary arteriograms and ventriculograms were performed by two of the investigators, who did not know the results of the ^{201}Tl studies. Differences between observed measurements were resolved by consensus. Significant CAD was defined as ≥70% diameter narrowing in one or more major vessels in one angiographic projection. Global and segmental wall motion abnormalities on the ventriculograms were noted. Abnormal left ventricular function was defined as a left ventricular ejection fraction <45% or the presence of dyskinesis, akinesis or hypokinesis in one or more ventricular segments.

Moderate CAD: To assess the effect of including patients with moderate CAD on the definition of the normal curve, a range curve was calculated from all patients without significant CAD, i.e., normal subjects and patients with moderate CAD.

A scintigram was considered abnormal if the patient's values dropped below the normal range at one or more points. The location of a coronary lesion was said to be concordant with the perfusion defect on the tomogram if the patient's perfusion curve fell below the lower limit of normal at one or more points in the distribution of the obstructed coronary artery.

Statistics: Sensitivity was defined as (true positives)/(true positives + false negatives). Specificity was (true negatives)/(true negatives ± false positives). Predictive accuracy of an abnormal test was (true positives)/(true positives + false positives). The false-positive rate was I minus the specificity. The data were analyzed by chi-square and Cochran's tests where appropriate.

Results

Safety

Dipyridamole was well tolerated by most of the patients in the study. There were no significant arrhythmias or episodes of severe angina pectoris. In most patients, systolic blood pressure decreased by 5-10 mm Hg and heart rate increased by 5-15 beats/mm during the infusion. About one-third of the patients complained of mild symptoms, such as dizziness, mild chest discomfort or nausea, which did not require any treatment or alteration in the protocol. Two patients were

given i.v. aminophylline for severe nausea or vomiting that occurred 5-10 minutes after the ^{201}Tl had been injected. The nausea and vomiting quickly abated after injection of the aminophylline (250 mg, iv.). Both of these patients had positive planar and tomographic images. In one patient, the dipyridamole infusion was discontinued and aminophylline was administered because of a 40-mm Hg decrease in systolic blood pressure. Normotension was promptly restored. This patient had severe left ventricular dysfunction (left ventricular ejection fraction of 18%). Three patients who were asymptomatic had 2-4 mm of flat or downsloping ST-segment depression during the dipyridamole infusion. The ST-segment depression disappeared spontaneously within 10 minutes after the dipyridamole infusion. None of the patients with unstable angina developed significant symptoms during the dipyridamole infusion.

Sensitivity, Specificity and Predictive Accuracy of ^{201}Tl: Comparison of Approaches

In the absence of quantitative analysis, tomographic imaging did not improve specificity or sensitivity significantly. With quantitative analysis the sensitivity was 90% and it was 76% without. Specificity was 96% and 66% with and without the quantitative analysis, respectively. The predictive accuracy of an abnormal tomographic ^{201}Tl scintigram interpreted with quantitative criteria was significantly greater ($p < 0.05$) than the predictive accuracy of a positive image obtained with the other two imaging approaches.

Interobserver Variability

When planar or tomographic ^{201}Tl images were interpreted using visual criteria, interobserver variability was 40% for tomographic images and 44% for planar images. Quantitative analysis of tomographic images eliminated interobserver variability.

Effects of Extent of CAD on Sensitivity

With planar scintigrams, sensitivity tended to increase with the extent of CAD, but the differences were not statistically significant. When tomographic images were interpreted with quantitative criteria, sensitivity was not related to the severity of CAD. Only three of the 52 CAD patients did not have either one coronary vessel with a 90% or greater obstruction or abnormal left ventricular function. Thus, the data concerning sensitivity of detecting CAD with ^{201}Tl scintigraphy were only applicable to patients with severe coronary obstructions.

Effects of Left Ventricular Function on Sensitivity

In patients with CAD who had abnormal ventricular function, the percentage of patients with positive ^{201}Tl scintigrams was significantly increased ($p < 0.05$) regardless of the imaging approach that was used. In CAD patients with normal left ventricular function, quantitative tomograms tended to be more sensitive in detecting CAD than visual interpretation of either planar or tomographic ^{201}Tl scintigrams.

Sensitivity and Specificity of ^{201}Tl Scintigrams in Patients with the Clinical Syndrome of Unstable Angina

In patients with the clinical syndrome of unstable angina, the sensitivity and specificity of diagnosing CAD was best with tomographic ^{201}Tl images if the interpretation was based on quantitative criteria.

Discordant Results

In 11 patients with CAD, the tomograms interpreted with quantitative criteria and planar images yielded discordant results. Eight patients had a positive tomogram and a negative planar image and three had a positive planar image and a negative tomogram. In two patients with two-vessel CAD, both tests were negative. In the eight patients with positive tomograms and negative planar images, the tomographic abnormalities were iii the left anterior descending artery in five, the circumflex artery in two and the dominant right coronary artery in one. In nine patients with normal coronary vessels, the results of the quantitative tomograms and planar images were also discordant. In eight, the tomogram was negative. Thus, when the quantitative tomographic images, scintigrams and planar images were discordant, 80% of the time the quantitative toniographic examination yielded the correct diagnosis.

Appendix C

Article title:	Quantitative Thallium-201 Single-Photon Emission Computed Tomography During Maximal Pharmacologic Coronary Vasodilation With Adenosine for Assessing Coronary Artery Disease
Authors:	Shigeiuki Nishimura, MD, John J. Mahmarian, MD, Terri M. Boyce, MS, CNMT, Mario S. Verani, MD,
Journal and year of publication:	Am J Cardiol 1991; 67: 1190-1194
Investigative site:	Baylor College of Medicine: and The Methodist Hospital, Houston, TX, USA
Objective:	To investigate the diagnostic usefulness of visual and quantitative thallium-201 tomography when combined with adenosine infusion in a large cohort of patients with concomitant coronary angiography.
Number of patients:	101

Demographics:
Coronary angiography was performed 6.0 ± 6.9 days before tomography in 59 patients, 6.2 ± 71 days after tomography in 40 patients and on the same day in 2 patients.

Patients had chest pain (53%) or shortness of breath (14%), risk stratification late after myocardial infarction (13%) and screening for coronary artery disease (20%) in patients unable to perform an exercise test because of associated peripheral vascular or neurologic disease. Most patients had a history of chest pain (67%), either typical (55%) or atypical (12%) for angina. Less common symptoms were dyspnea (14%), palpitation (3%), syncope (1%) and dizziness (1%). Fourteen percent of the patients had no cardiac or respiratory symptoms and were being evaluated before a peripheral vascular surgical procedure.

Patients had a mean age of 60 ± 11.1 years (range 33 to 83).

Inclusion criteria: Not described.

Exclusion criteria: Patients with second- or third-degree atnoventricular (AV) block without a functioning ventricular pacemaker, bronchospastic respiratory condition, sick sinus syndrome, recent myocardial infarction (<I month), hypotension (rest systolic blood pressure <90 mm hg), severe hypertension (rest systolic pressure >180 mm Hg or diastolic pressure >120 mm Hg) and

severe congestive heart failure (New York Heart Association class IV).

Patients were also excluded if they had a prior history of coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or valvular heart disease

Dose: Adenosine was infused in the first 30 patients with the infusion rate from 50 to 140 ug/kg per min, with the highest dose maintained for 4 min. In the last 71 patients, adenosine was infused at a constant rate of 140 ug /kg per min for a total of 6 min. With both infusion methods, ^{201}Tl (3 to 3.5 mCi) was injected in a contralateral vein 3 mm before the adenosine infusion was terminated.

Imaging and data acquisition: Imaging began 5 min after termination of the adenosine infusion; a large field of view, single-crystal, rotating gamma camera equipped with a high resolution and parallel hole collimator were used. Image acquisition was performed over an 180 ° arc from the 450 left posterior oblique to the 450 right anterior oblique position, at 6~ intervals and for 40 s/image. Images were stored on a 2-gigabyte laser disk for analysis.

Transaxial reconstruction used a back projection technique with a Butterworth (order of 5) high pass filter with a low pass window at a 50% cutoff. Reconstructed tomographic slices of 6-mm thickness were then reoriented in the standard short, horizontal long and vertical long axes for visual and quantitative analysis, as previously reported from our laboratory. Redistribution images were obtained 4 h after the thallium injection.

Visual analysis of tomographic slices: Visual assessment of the tomographic slices was performed by two experienced observers who were unaware of the results of coronary angiography and the ECG findings at rest or during adenosine infusion.

Slices were displayed sequentially in all three cardiac planes to assess myocardial perfusion in each vascular territory. Perfusion defects were analyzed for the presence of complete, partial or no redistribution 4 h after thallium injection. The vascular territories of the three major coronary arteries were assigned as follows: the anteroseptal, anterior and anterolateral walls to the left anterior descending coronary artery; the inferior, posterior and posteroseptal walls to the right coronary artery and the lateral and posterolateral walls to the left circumflex coronary artery. Pure apical defects were considered abnormal but were not assigned to any individual coronary vessel.

Computer quantification of tomographic images: ^{201}Tl tomographic images were quantified by using a computerized two dimensional polar map of the three-dimensional myocardial radionuclide activity. The map was generated through use of a circumferential profile analysis whereby pixel count activity from the center to the outer boundary of each short-axis slice was computed along radians spaced at 6 ° intervals over 360°. The count activity for each radian was determined as the highest average activity for each group of three adjacent pixels. Individual slices from the cardiac apex to base were displayed as concentric rings in the polar map. Left ventricular apical limits were defined from the short- and vertical long-axis slices and displayed

in the center of the polar map.

The map of each patient was statistically compared with **a** normal data bank derived from 27 normal subjects (13 men, 14 women, mean age 66 ± 12 years) who underwent adenosine thallium-201 tomography in our laboratory. Fifteen of these subjects were at low risk (<5% likelihood) for having coronary artery disease in that they had no chest pain, no prior cardiovascular history, a normal rest ECG, fewer than three risk factors and a visually normal tomographic study. The remaining 12 subjects had atypical chest pain and normal coronary arteriography.

A pixel in a patient's polar map was considered abnormal if its count activity was >2.5-SD below the mean count for the corresponding pixel in the normal data bank. Quantitative ^{201}Tl tomographic defect size was expressed as the percent of abnormal pixels in the total polar map. The initial tomographic polar maps obtained after the adenosine infusion were used to quantify perfusion defects.

Designation of individual coronary vascular territories was identical to that used for visual analysis of tomographic slices. As a result of overlap in boundaries between vascular territories, a focal perfusion defect that occurred predominantly in one vascular region but extended only partially into another adjacent territory was considered to represent single-vessel stenosis. A patient's polar map was considered abnormal if a 3% focal perfusion defect was found within a given vascular territory. This cutoff is similar to the one we have previously derived for dipyridamole and exercise SPECT and has afforded high sensitivity and specificity for detection of coronary artery disease.

The quantitative polar maps were used to assess the presence and extent of coronary artery disease. However, the occurrence of redistribution was determined primarily from the visual analysis of the individual tomographic slices.

Blinded read: Construction and interpretation of polar maps were done by two experienced investigators who did not know the clinical or angiographic findings.

Statistics: Hemodynamic variables in patients were compared with use of paired ***t*** tests. When a normal distribution was not present, the Wilcoxon signed-rank test was used. All comparisons of sensitivity and specificity were made with use of chi-square analysis, as was analysis of redistribution in perfusion defects among patients with and without infarction. The Wilcoxon rank-sum test was used to statistically compare the size of the perfusion defect in patients with coronary artery disease of variable extent, The data are expressed as mean values ± SD. A p value < 0.05 was considered significant.

RESULTS

Sensitivity

The sensitivity for detecting the presence of coronary artery disease was similar with visual (84%) versus quantitative (90%) analysis of the tomograpbic images. The sensitivity was also

similar for both methods when patients were analyzed at different levels of stenosis severity (>50% and _70%) and according to the presence or absence of myocardial infarction. Sensitivitywas significantly higher in patients with (96%) than in those without (78%) prior infarction only when visual tomographic analysis was used.

Effect of beta-blockers
Patients on beta-blocker therapy were analyzed separately because they had a lower heart rate and rate-pressure product during adenosine infusion than did those not receiving a beta-blocker. The sensitivity by quantitative analysis was not significantly different for patients who were (80%) or were not (89%) taking a beta-blocker.

Effect of imaging sequence (scintigraphy vs angio). To assess the influence of post-test referral bias on sensitivity and specificity, we separately analyzed patients who underwent thallium tomography before or after coronary angiography. The sensitivity by quantitative analysis was similar for both groups (86% vs. 88%, respectively).

However, the specificity by quantitative analysis tended to be lower in the 12 patients who had tomography before (83%) than in the 19 who had tomography after (95%) coronary angiography.

Effect of extent of vessel involvement
In the subgroups without myocardial infarction, quantitative analysis identified 76%, 86% and 90% of patients with single-, double- and triple-vessel disease, respectively. There was a higher sensitivity for detecting coronary disease in patients without infarction who had multi-vessel versus single-vessel involvement with use of the visual but not the quantitative method. Multi-vessel disease was correctly predicted in 66% of patients.

Effect of individual vessel involvement
In patients with single-vessel disease, 81% of arteries with >50% stenosis and 91% of those with _70% stenosis were correctly identified by quantitative analysis. In double-vessel disease, the corresponding values were 68% and 67%, and in triple-vessel disease 65% and 75%, respectively.

The sensitivity and specificity for detecting individual vessels were not significantly different between the visual and quantitative methods. The sensitivity for detecting >50% stenoses in the left anterior descending and right coronary arteries tended to be higher than that for left circumflex artery stenoses by both methods of tomographic analysis but did not reach statistical significance.

Redistribution patterns in patient subsets.
Tomographic images were visually analyzed to assess temporal (4-h) changes in perfusion defects in all three vascular territories for each patient. The 86 abnormal vascular territories in the 58 patients with true positive perfusion defects were scored as follows: 36 (42%) with complete, 34 (39%) with partial and 16 (19%) with no redistribution. In the 34 patients without

previous infarction, 32 (60%) of the 53 abnormal vascular territories were interpreted as showing complete redistribution, 15 (28%) as showing partial and 6 (11%) as showing no redistribution. The 24 patients with infarction demonstrated complete redistribution in 4 (12%), partial redistribution in 10(30%) and no redistribution in 19 (57%) of the 33 abnormal vascular territories. Patients without infarction had significantly more scintigraphic evidence of redistribution than did those with infarction (88% vs. 42%, respectively; $p < 0.05$).

Effect of perfusion defect size.

Perfusion defect size increased with more extensive coronary artery disease. The mean tomographic defect size in the 31 normal subjects was 1.8 ± 4.3% and usually conformed to a scattered pattern. The mean defect size observed in patients with triple-vessel disease (24.4 ± 20%) was significantly larger than that seen in those with single-vessel disease (11.9 ±16.8%, $p < 0.05$). Perfusion defect size was not significantly different between patients with single- and double-vessel disease or between those with double- and triple-vessel disease.

Specificity

Specificity was slightly higher by quantitative than by visual analysis (90% vs. 84%, respectively; p = NS).

Appendix D

Title:	Assessment of Coronary Artery Disease Using Single-Photon Emission Computed Tomography with Thallium-201 During Adenosine-Induced Coronary Hyperemia
Authors:	Abdulmassih S. lskandrian, MD, Jaekyeong Heo MD, Thach Nguyen, MD, Sally G. Beer, MD, Virginia Cave, RN. ,David Ogilby, MD, William Untereker, MD, and Bernard L. Segal, MD
Journal and year of publication:	Am J Cardiol 1991;67:1190—1194
Investigative site:	Philadelphia Heart Institute, Presbyterian Medical Center, Philadelphia, PA, USA
Objective:	To examine the results of SPECT with ^{201}Tl during adenosine-induced coronary hyperemia in 148 patients who also underwent coronary angiography.
Number of patients:	148
Demographics:	The patient population consisted of 85 men and 63 women of average age 63 years. Among them were patients with systemic hypertension (43%), diabetes mellitus (18%) and previous myocardial infarction (25%).
Inclusion criteria:	Patients with the mean time interval between coronary angiography and thallium study 7 days; in 108 patients the thallium images were obtained within 1 week of coronary angiography.
Exclusion criteria:	Patients with recent myocardial infarction, unstable angina pectoris, greater than first-degree atrioventricular block or active bronchospastic pulmonary disease, and those taking theophylline containing medications at the time of the study.
Dose:	Intravenous infusion of adenosine was initiated at a dose of 0.14 mg/min/kg body weight using an infusion pump and continued for a total of 6 minutes.

At the end of the third minute of infusion, a 3 to 3.5 mCi (111 to 130 MBq) dose of ^{201}Tl was injected intravenously.

Imaging and data acquisition: SPECT imaging was begun within 5 minutes and again at 4 hours after thallium injection. In some patients re-injection delayed images were obtained 20 minutes after the additional injection of 1 mCi (37 MBq) of ^{201}Tl. There were no special selection criteria in these patients because the re-injection method was used routinely. The extent of the perfusion abnormality was estimated as the percentage of the total area and the severity score was derived from the extent and the number of standard deviations below the mean normal for each point within the abnormal area.

Blinded read: Not described.

Statistics: Data were presented as mean with standard deviation when appropriate. The 95% confidence intervals were used when indicated, Chi-square analysis and Student's t test were used for comparison. A p value <0.05 was considered statistically significant.

RESULTS

Diagnostic Sensitivity and Specificity

The sensitivity and specificity were 92 and 88%, respectively (95% confidence intervals were 86 to 96% and 59 to 100%, respectively). Of the 2 patients with normal coronary angiograms and abnormal images, 1 was thought to have hypertrophic cardiomyopathy. The sensitivity was 87% in the 54 patients with 1-vessel CAD (47 of 54 patients had abnormal results), 92% in the 37 patients with 2-vessel CAD (34 of 37 patients had abnormal results) and 98% in the 41 patients with 3-vessel CAD (40 of 41 patients had abnormal results). Perfusion defects were seen in territories of 73% of diseased arteries. The size of the perfusion abnormality was quite variable: It was 24 ± 12% in patients with 1-vessel CAD, and 26 ± 12% in patients with 2- and 3-vessel CAD (difference not significant). In patients without prior myocardial infarction, the sensitivity was very high. Sensitivity in women was 87% (45 of 52 women with CAD had abnormal images) and, similarly, sensitivity in patients >65 years was 90% (65 of 72 patients had abnormal images). Adverse effects were similar in elderly patients and younger patients.

Effect of re-injection

In the 132 patients with CAD, 12 had normal thallium images, 49 had reversible perfusion defects, 29 had fixed defects and 42 had both fixed and reversible defects. The mean number of defects was 8.3 segments per patient. In patients with CAD and no prior myocardial infarction, who also had abnormal thallium images, 73 patients had conventional 4-hour delayed imaging and 16 patients had reinjection delayed imaging. There were 611 segments with perfusion defects in the former group (mean 8.5 per patient) and 102 in the latter group (6.4 per patient).

The perfusion defects were considered fixed in 99 of 611 segments (16%) in patients with conventional delayed imaging, whereas all defects were interpreted as reversible in the re-injection group ($p<0.0001$).

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/s/

Joseph Zolman
7/23/04 02:16:32 PM
MEDICAL OFFICER

Zili Li
7/23/04 02:38:55 PM
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NDA 18-150/SE1-019
NDA Supplement

Medical Team Leader's Memorandum

Date submitted: September 30, 2003
Due Date: July 30, 2004
Memo completed: July 23, 2004

Trade Name: Thallous Chloride Tl-201 Injection
Active Ingredient: Thallous Chloride Tl-201
Dosage Strength: 1 mCi/mL
Dosage: 1-2 mCi for planar myocardial imaging
2-3 mCi for SPECT myocardial imaging
Route of Administration: IV Infusion
Proposed Indications: Thallous Chloride Tl 201 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.

Materials Reviewed:

- Original NDA supplement (September 30, 2003)
- Request for a waiver from the requirement to conduct pediatric study (March 2, 2004);
- Package Insert Update (March 10, 2004)
- Package Insert Update (June 11, 2004)
- Package Insert Update (July, 8, 2004)

1. Executive Summary:

The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA efficacy supplement (NDA 18-150/SE1-019). I recommend that this NDA receive **Approval** action pending the final agreement on proposed changes to the product label. My rationale for this recommendation is as follows:

1. Thallous Chloride Tl-201 (thallium), in conjunction with a pharmacologic stress agent (either IV Persantine or Adenoscan), have been found by the Division of Cardio-Renal Drug Products to be safe and effective when they are used to evaluate patients with known and suspected coronary artery disease and who cannot exercise adequately;
2. I found that the data used to support the Agency's prior decisions is still compatible with the current standards to approve similar imaging drugs for the same indication. In particular, exercise stress thallium imaging was employed as a comparator, and coronary arteriography as the reference standard. All tests (thallium imaging and coronary arteriography) were read blindly;
3. Although the sensitivity and specificity of thallium pharmacologic stress test from some of the original trials might appear to be sub-optimal, they were comparable to

that of thallium exercise stress test, which has a well defined clinical utility in evaluating patients with known or suspected coronary artery disease;

4. A meta-analysis presented by the sponsor did not cast any doubt on the performance of thallium pharmacologic stress test in evaluating the patients with known or suspected coronary artery disease;
5. All marketed thallium imaging products are considered chemically identical (Appendix A). While thallium imaging product of this sponsor may not be the one used in the original clinical trials, there is little evidence to suggest that thallium imaging products from different NDA holders would act differently in a clinically significant manner.

Before an Approval action, however, I recommend that:

- Pharmacologic stress indication be limited to the patients who cannot exercise adequately since thallium pharmacologic stress test has not shown an "added" benefit in terms of sensitivity and specificity, compared to that of thallium exercise stress test;
- A statement regarding the risk of pharmacologic stress be added to the WARNING section of the product label;
- Appropriate reference to the Package Insert of the approved pharmacologic stress agents should be made in the Adverse Event Section of the thallium labeling regarding the safety information.

2. Scientific and Regulatory Background:

Currently there are three commercially available FDA-approved myocardial perfusion imaging agents in the United States, i.e., Thallous Chloride Tl 201, Cardiolite and Myoview, and Thallous Chloride Tl 201 has three different NDA holders. Table 1 summarize myocardial perfusion imaging agents approved under the NDA process. In addition, there is one additional Thallous Chloride Tl 201 product approved under the ANDA process in 2001 (ANDA #75-569, Mount Sinai Medical Center).

Table 1. List of myocardial perfusion imaging agents approved under NDA process

NDA #	17-806	18-150	18-548	19-785	20-372
Trade Name	Thallous Chloride Tl 201	Thallous Chloride Tl 201	Thallous Chloride Tl 201	Cardiolite	Myoview
Active Ingredient				Tc 99m sestamibi	Tc 99m tetrosmin
Year of Original NDA Approval	1977	1979	1982	1990	1996
Name of the sponsor	Bristol-Myers Squibb medical imaging	Mallinkrodt	Bracco	Bristol-Myers Squibb medical imaging	GE Health
Parmacologic Stress Indication	No	No	No	Yes (1995)	Yes (2001)

The approved indications for Thallous Chloride Tl-201 that is currently marketed by Mallinckrodt (the sponsor) are as follows:

- *Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging using either planar or SPECT (Single Photon Emission Computed Tomography) techniques for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the perfusion defect.*

- *Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct to the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).*

On September 30, 2003, the sponsor submitted a NDA efficacy supplement (SE1-019) that seeks the Division's approval for a new indication, i.e.,

> *Thallous Chloride Tl-20 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.*

Since no portion of this NDA supplement relies on information that has been obtained by right of reference, the sponsor cited the section of 505(b)(2) of the Federal Food, Drug and Cosmetic Act, referring to the Agency's prior approval of IV Persantine and Adenoscan.

The product label for IV Persantine (NDA 19-817) says, in part:

> *IV Persantine is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.*

The product label for Adenoscan (NDA 20-059) says, in part:

> *Intravenous Adenoscan is indicated as adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.*

The sponsor has argued that the use of Thallous Chloride Tl-201 as a myocardial perfusion imaging agent, in conjunction with a pharmacologic stress agent, should be considered as an approved indication.

> ***Reviewer's Comments:*** *While the sponsor's rationale appears to be reasonable, we have solicited an official opinion for the Division of Cardio-Renal Drug Products since both pharmacologic agents mentioned in the supplement were approved in that Division.*
>
> *In his memo dated May 6, 2004, Dr. Stockbridge, the acting division director, provided a summary of analysis for those two NDAs, and agreed that "it seems reasonable to conclude that thallium imaging employed in pharmacologic stress*

testing with persantine or Adenoscan, should be considered effective and adequately safe".

Actually this Division had expressed a similar view as early as 1995 when pharmacologic stress indication was added to Cadiolite product label. In her memo, Dr. Love, then the division director, stated that "in the Division of Medical Imaging, Cardiolite was approved in comparison to thallium and the two are considered to be at least comparable".

Both IV Persantine and Adenoscan were approved approximately 10-15 years ago. While agreeing with the Agency's prior decision, I felt that it is also important to reexamine the key components of the original clinical trials to ensure that they still meet the currently standards for an approval.

3. Data Source and Method of Review:

Through the Freedom of Information Act, the Sponsor obtained the copies of division director memo, primary medical officer's reviews and statistical reviews for NDA 19,817 (IV Persantine) and NDA 20-059 (Adenoscan). The sponsor also submitted the current product labels of those two products.

In addition, the sponsor also submitted the results of a meta-analysis of all relevant published clinical studies involving thallium pharmacologic stress tests.

I have asked the primary medical reviewer and statistical reviewer to focus their review on the meta-analysis performed by the sponsor (please see their reviews for detailed information). Ensuring conformity of the original clinical trials with the current standards is the subject of this review.

4. The Efficacy Review:

A. Original Clinical Studies:

The current IV Persantine product label states:

> In a study of about 1100 patients who underwent coronary arteriography and IV Persantine® assisted thallium imaging, the results of both tests were interpreted blindly and the sensitivity and specificity of the Persantine® thallium study in predicting the angiographic outcome were calculated. The sensitivity of the Persantine® test (true positive Persantine® divided by the total number of patients with positive angiography) was about 85%. The specificity (true negative divided by the number of patients with negative angiograms) was about 50%.
>
> In a subset of patients who had exercise thallium imaging as well as Persantine® thallium imaging, sensitivity and specificity of the two tests.

The current Adenoscan product label states:

In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (≥50% reduction in the luminal diameter of at least one more vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiograms) was 54% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity were 37% to 71%.

Reviewer's Comments: *In addition to the product labeling information, I also have reviewed the copies of the medical officer's reviews, statistical reviews and division director memo for these two pharmacologic stress agents under NDA 19-817 and 20-059. As stated early, that information were obtained by the sponsor via the Freedom of Information Act and submitted with this NDA supplement.*

For IV Persantine assisted thallium imaging, the primary efficacy analysis was based on a subgroup of 146 patients who had all 3 tests (coronary angiography, thallium 201/exercise, and thallium 201/IV Persantine) from a large clinical study (Boehinger Ingelheim Persantine Imaging Study, n = 1096). For Adenoscan, the primary efficacy analysis was based on 196 patients from two clinical studies (C-5A and C-5B), and all patients also had the 3 tests.

Those were prospectively designed studies that enrolled the patients with know and suspected coronary disease and who were referred for a coronary angiography. Exercise stress thallium imaging was used as an appropriate comparator (control) to pharmacologic stress thallium imaging. All thallium images were read blindly, and compared to that of coronary aniography (also read blindly) to determine the sensitivity and specificity of different thallium imaging techniques, i.e., exercise vs. pharmacologic stress.

It is apparent that the original clinical trials used to support the Agency's prior decisions still meet the current standards for approving similar imaging agents for the same indication. Table 2 showed the sensitivity and specificity and number of patients used in the primary analyses by type of stress technique (exercise vs. pharmacologic stress).

Table 2. Sensitivity and specificity of thallium imaging by type of the stress technique

	IV Persantine Trial		*Adenoscan Trials*	
	Persantine Thallium	*Exercise Thallium*	*Adenoscan Thallium*	*Exercise Thallium*
Sensitivity	*86.4 (n=118)*	*86.4 (n=118)*	*64 (n=156)*	*64 (n=156)*
Specificity	*50 (n=28)*	*50 (n=28)*	*54 (n=37)*	*65 (n=37)*

There are two questions to be answered here:

- *What is the comparative efficacy of exercise vs. pharmacologic stress thallium imaging tests? and,*
- *What are the most reliable estimates for sensitivity and specificity of a thallium pharmacologic stress test?*

Data presented here suggest, with a reasonable degree of certainty, that pharmacologic stress thallium imaging, is comparable to that of exercise stress thallium imaging. Since the data have only demonstrated a comparative but not an "added" value of a thallium pharmacologic stress test, the Agency was correct in limiting the use of thallium pharmacologic stress test to only those patients who cannot exercise adequately.

Someone might argue that the sensitivities of Adenoscan stress test and the specificity of both IV persantine and Adenoscan stress test were low. The numbers appears to be low from Table 2 but the main objective of those analyses was to demonstrate the comparative value of pharmacologic stress vs. exercise stress thallium imaging tests. The sensitivity and specificity estimated from those studies might not necessarily be the most stable estimates because of the small sample size. This issue will be addressed in the next section by reviewing the results of a meta-analysis of all relevant published literatures.

B. Literature Data:

The purpose of this literature review (meta-analysis) is not to demonstrate efficacy of thallium pharmacologic stress test. I consider this issue has been successfully resolved because of the Agency's prior decision and the reconfirmation that data used to support that decision still meet the current scientific standards.

The sole purpose of this literature review, in my view, is to ensure that current efficacy information would not cast doubt on the performance of thallium pharmacologic stress test in terms of sensitivity and specificity.

The sponsor submitted a final report for the meta-analysis, including study objectives, design, inclusion/exclusion criteria, study endpoints, statistical analysis and results. That information was reviewed by Dr. Zolman, the medical reviewer, and Dr. Sobhan, the statistical reviewer (please see their review for detailed information). All studies that

were published between January 1982 and September 2002 in English concerning IV Persantine or Adenoscan stress test were identified and then selected based on the following main inclusion criteria:

- Patients with known or suspected coronary artery disease
- Patient having both thallium imaging stress test and coronary angiography
- All tests were read blindly
- Sensitivity and specificity were the endpoints of the study

The major exclusion criterion was the patients with prior history of coronary artery bypass graft surgery (CABG).

Of 51 articles identified, 25 were included in the meta-analysis with a total of 2,614 patients. Of those, 1,217 patients (from 14 studies) received IV Persantine, and 1,397 patients received Adenoscan. Sensitivity and specificity of thallium imaging were calculated separately for two pharmacologic stress agents using both fixed effects model and random effect model. Two study subgroups were established for each stress agent based on the severity of coronary stenosis as determined by angiography luminal area narrowing either $\geq$ 50% or $\geq$ 70%.

Table 3 showed sensitivity and specificity of thallium pharmacologic stress test under a random effects model by stress agent and criteria used to define coronary artery disease. The results showed the sensitivity of thallium pharmacologic stress test is between 89% and 93% regardless of pharmacologic agents used or criteria used to define coronary artery disease (i.e., 50% or 70% stenosis). The lower limit of 95% CI was approximately 85%. The estimates of specificity, however, varied significantly (from 64% to 100%). While the specificity estimates are not as stable as that of the sensitivity, they are, in general, higher than that from the original clinical trials of each pharmacologic stress agent.

The sensitivity and specificity results calculated under the fixed effects model were similar to that of the random effects model (data not shown).

Table 3. Sensitivity and specificity of thallium pharmacologic stress test by pharmacologic stress agent and criteria used to define coronary artery disease (meta-analysis of relevant studies, the random effects model)

Criteria used to define coronary artery disease	IV Persantine		Adenoscan	
	Sensitivity [95%CI]	Specificity [95%CI]	Sensitivity [95%CI]	Specificity [95%CI]
≥50% stenosis	89.3 [85.0,93.6] (n=227)	64.2 [49.7, 87.0] (n=77)	88.8 [86.7, 90.7] (n=)	88.6 [82.4, 94.7] (n=)
≥70% stenosis	90.6 [87.6, 93.6] (n=694)	76.6 [71.1, 82.1] (n=219)	93.2% [88.0, 98.5] (n=98)	100% [86.8, 100] (n=14)

Reviewer's Comments: *Meta-analysis, especially the one with individual studies as the unit of analysis, has many limitations. The Agency rarely accepts the data presented from meta-analysis as the key evidence to support the efficacy of a drug product. After the efficacy is demonstrated, however, the meta-analysis could play a limited role in estimating the magnitude of the drug effect.*

It appears that the sponsor has made a reasonable effort in identifying the appropriate studies to be included in the meta-analysis by prospectively defining the inclusion and exclusion criteria. In particular, the reasons for excluding certain studies were well articulated. In primary medical officer's review, Dr. Zolman noted that the lowest sensitivity and specificity of the thallium pharmacologic stress test from the included studies were 79% and 47%, respectively. There is little evidence that the sponsor purposely excluded the studies with low sensitivity and specificity.

The studies that were included in the meta-analysis appear to have adequate documentation, allowing the assessment of study design and conduct. Those studies, at least on paper, appear to be consistent with the two key study design requirements, i.e., a blinded read of all images and coronary angiography as the gold standard.

One of the key concerns regarding the meta-analysis is the publication bias. The sponsor did attempt to address this issue by using a statistical modeling. While the potential impact of publication bias cannot be ruled out, I have little concern in this case given the number of studies included and the objective of the meta-analysis.

In summary, the sensitivity and specificity of thallium pharmacologic stress test estimated from the meta-analysis appear to be higher than that observed from the original clinical studies used to support the Agency's prior decision. The analysis casts no doubt on the performance of thallium pharmacologic stress test as a tool in evaluating of patients with known or suspected coronary artery disease and who cannot exercise adequately.

5. Safety Review:

The current Adenoscan product label states:

ADVERSE REACTIONS

The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Flushing	44%
Chest discomfort	40%
Dyspnea or urge to breathe deeply	28%
Headache	18%
Throat, neck or jaw discomfort	15%
Gastrointestinal discomfort	13%
Lightheadedness/dizziness	12%
Upper extremity discomfort	4%
ST segment depression	3%
First-degree AV block	3%
Second-degree AV block	3%
Paresthesia	2%
Hypotension	2%
Nervousness	2%
Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:
Body as a whole: back discomfort; lower extremity discomfort; weakness.
Cardiovascular System: nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm Hg).
Central Nervous System: drowsiness; emotional instability; tremors.
Genital/Urinary System: vaginal pressure; urgency.
Respiratory System: cough.
Special Senses: blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort.

The current IV Persantine product label states:

ADVERSE REACTIONS

Adverse reaction information concerning intravenous Persantine® (dipyridamole USP) is derived from a study of 3911 patients in which intravenous Persantine® was used as an adjunct to thallium myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.
Serious adverse events (cardiac death, fatal and non-fatal myocardial infarction, ventricular fibrillation, asystole, sinus node arrest, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia, seizures, anaphylactoid reaction, angioedema and bronchospasm) are described above (see WARNINGS).
In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).

Adverse reactions occuring in greater than 1% of the patients in the study are shown in Table 1:

Table 1 Drug-Related Adverse Reactions (%) Occurring in Greater than 1% of PatientsIncidence (%) of Drug-Related Adverse Reaction Adverse Reactions

Chest pain/angina pectoris	19.7
Headache	12.2
Dizziness	11.8
Electrocardiographic Abnormalities/ST-T changes	7.5

Electrocardiographic Abnormalities/Extrasystoles	5.2
Hypotension	4.6
Nausea	4.6
Flushing	3.4
Electrocardiographic Abnormalities/Tachycardia	3.2
Dyspnea	2.6
Pain Unspecified	2.6
Blood Pressure Lability	1.6
Hypertension	1.5
Paresthesia	1.3
Fatigue	1.2

Less common adverse reactions occurring in 1% or less of the patients within the study included:
Cardiovascular System: Electrocardiographic abnormalities (0.8%), arrhythmia (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see WARNINGS), bradycardia (0.2%), myocardial infarction (0.1% see WARNINGS), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia (0.03% see WARNINGS), heart block (0.03%), cardiomyopathy (0.03%), edema (0.03%).
Central and Peripheral Nervous System: Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).
Gastrointestinal System: Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).
Respiratory System: Pharyngitis (0.3%), bronchospasm (0.2% see WARNINGS), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).
Other: Myalgia (0.9%), back pain (0.6%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthenia (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%), earache (0.1%), tinnitus (0.1%), vision abnormalities unspecified (0.1%), dysgeusia (0.1%), thirst (0.03%), depersonalization (0.03%), eye pain (0.03%), renal pain (0.03%), perineal pain (0.03%), breast pain (0.03%), intermittent claudication (0.03%), leg cramping (0.03%). In additional postmarketing experience, there have been rare reports of diarrhea, allergic reaction including urticaria, pruritus, dermatitis and rash. Mesenteric ischemia and mesenteric infarction have also been observed in association with intravenous Persantine® (dipyridamole USP) administration.

Reviewer's Comments: *All safety information was provided from IV Persantine and Adenoscan's product labels. Dr. Zolman reviewed adverse events reported from the literature data and found no additional safety issues. I see little need to conduct additional safety analyses because the risk and benefit ratio is unlikely to change for the following reasons:*

- *It has been widely accepted that thallium pharmacologic stress test is of great clinical value to those patients who cannot exercise adequately;*
- *Current safety information has already addressed many serious adverse events that could occur with the administration of pharmacologic agents and thallium.*

6. Clinical Performance of Different Thallium Products:

The sponsor acknowledged that its product may not be the one that was used in the original clinical trials to support the efficacy of thallium pharmacologic stress test, but argued that there should be little concern over clinical performance of its product because all thallium products are chemically identical.

Reviewer's Comments: *I discussed this issue with our chemistry team leader who then confirmed the sponsor's statement (please see Appendix A). Clinically,*

I see little evidence that would suggest a significant difference in diagnostic performance or safety profile of different thallium products.

7. Labeling Review:

In the original NDA supplement submission dated September 30, 2003, the sponsor requested two additions to the current product label:

- Thallous Chloride Tl 201 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;
- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

On March 10, 2004, the sponsor added new clinical trial and safety information to the product label in responding to FDA's requests stated in the 74-day filing letter dated December 12, 2003.

Reviewer's Comments: *I agree with Dr. Zolman's recommendation that the new pharmacologic stress indication should be limited to patients who cannot exercise adequately. I also agree with the sponsor's new addition of a warning statement regarding potential risk of pharmacologic stress. This statement is identical to the one used in Myoview's product label.*

It appears that the sponsor misunderstood the Division's request regarding updating clinical trial information. The sponsor created a Clinical Study section and provided a summary for all indications. Since this NDA supplement is limited to pharmacologic stress indication, it is beyond the scope of this review to comment on the clinical trials that were conducted to support other approved indications.

I have communicated this comment to the sponsor who later amended this sNDA with a newly proposed labeling with no clinical trial information.

It is a challenge to update Adverse Events section of thallium product label because it involves two pharmacologic stress agents and the majority of the adverse events, especially the serious ones, are most likely to be caused by the pharmacologic agents rather than thallium.

I recommend an approach that only includes a key warning statement and then refer the readers to the Package Insert of approved pharmacologic stress agents for more information. Please refer to Appendix B regarding my response to the label changes proposed by the sponsor.

8. Pediatric studies:

The sponsor has requested a full waiver from the requirement to conduct pediatric studies relating to efficacy supplement for the following two reasons:

- Scintigraphic imaging of the myocardium using thallium injection and approved pharmacologic stress agents is very rarely used in patients under the age of 18 years; and
- The safety and effectiveness of the two agents that are approved for thallium pharmacologic stress imaging, Adenoscan and IV persantine, has not been established in a Pediatric Population

Reviewer's Comments: *By citing the data provided by* [redacted] *the sponsor estimated that no more than 500 pediatric patients undergone pharmacological stress studies using thallium in the United States for a two-year period between July 2001 and June 2003.*

Since the sponsor did not provide information on how the data is generated, I cannot make any reasonable assessment on the validity of the sponsor's conclusion at this time. While I agree with the sponsor's second argument that the two referenced pharmacologic agents are not approved in the pediatric population, these products are currently being used off-label for this purpose in the pediatric population. I recommend granting a deferral. Based upon the fact that pharmacologic stress agents are not approved for use in the pediatric population, deferral is granted until 5 years after the approval of any pharmacologic stress agent in the pediatric population in the United States.

9. Recommendation:

I recommend an **Approval** action for this NDA supplement pending the final agreement on the proposed changes made to the current product labeling. The sponsor should also be notified of our decision with regard to its request for a full waiver from the requirement to conduct a pediatric study.

Zili Li, MD, MPH
Medical Team Leader

Concur:

Sally Loewke, MD
Deputy Division Director

Addendum 7/23/04:

1. In an e-mail dated 7/20/2004, Ms. Kim Dettelback from the Office of Chief Counsel concurred the recommended approach of referencing to the Package Insert of approved pharmacologic agents;
2. On 7/21/2004, the sponsor provided a letter, agreeing on the proposed changes proposed by the Division to the product labeling in Appendix B;
3. On 7/21/2004, Ms. Diane Smith and I had a t-con with the sponsor, providing a preliminary comment with regard to deferring the pediatric study as recommended in this memo. The sponsor expressed no objection to our comment.

Appendix A Chemistry Team Leader's Comment

Comparison of U.S. Thallous Chloride Tl 201 products:

There are 4 ^{201}TlCl products marketed in the U.S. (BMS, Malinckrodt, Amersham and Bracco). All 4 have identical formulations, consisting of ^{210}TlCl (1 mCi/mL) in 0.9% sodium chloride with 0.9% benzyl alcohol as preservative.

The following table compares the impurity profiles of the above ^{201}TlCl products:

	NDA	^{201}Tl	^{200}Tl	^{202}Tl	^{203}Pb
BMS	17-806	• 98%			
Mallinckrodt	18-150	"			
Medi-Physics	18-110	"			
Bracco	18-548	• 97%			

Radionuclidic impurities are expressed as a percentage of ^{201}Tl at calibration.

There is only slight variability in the impurity profiles, and all meet the USP standards in theUSP monograph for Thallous Chloride Tl 201 Injection.

APPEARS THIS WAY
ON ORIGINAL

11 page/s of draft labeling was/were removed from this portion of the review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zili Li
7/23/04 02:37:17 PM
MEDICAL OFFICER

Sally Loewke
7/23/04 03:00:23 PM
MEDICAL OFFICER
I concur with Dr. Li's recommendation. As with other approved imaging products for this indication, this label will not specifically identify the pharmacologic stress agents by name.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA:	18-150 (SE1-019)
Name of Drug:	Thallous Chloride T1-201 Injection
Indication:	Evaluation myocardial ischemia with rest and stress techniques.
Sponsor:	Mallinckrodt Inc.
Date of Submission:	09/30/2003
Project Manager:	Diane Smith, HFD-160
Clinical Reviewer:	Joseph Zolman, M.D., HFD-160
Clinical Team Leader:	Zili Li, M.D., HFD-160
Statistical Reviewer:	Mahboob Sobhan, Ph.D., HFD-715
Statistical Team Leader:	Michael Welch, Ph.D., HFD-715
Biometrics Div. Director:	Edward Nevius, Ph.D., HFD-715

Key Words: NDA Review, Meta-analysis, Fixed and Random Effects Models.

1. Introduction

This NDA supplement is in support of the Sponsor's two proposed changes in the package insert for the NDA approved drug, Thallous Chloride, T1-201. Currently, two pharmacologic stress agents (IV Persantine and Adenoscan) are used as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease (CAD) in patients who cannot exercise adequately. In this submission, the Sponsor provided the diagnostic efficacy of IV Persantine and Adenosine stress used in conjunction with Thallium T-201 in the detection of CAD. The diagnostic efficacy was evaluated by a single estimator (sensitivity and specificity) from a meta-analysis of peer reviewed articles published between 1982 and 2002.

This review will focus on the statistical methods used in the analysis and the robustness of a single estimator from such a systematic review. The materials reviewed included the meta-analysis result and the corresponding literature articles. No electronic data was provided by the sponsor.

2. Sponsor's Meta-Analysis

The Sponsor selected articles based on the following criteria: (1) Studies conducted in patients with known or suspected coronary artery disease, (2) Patients underwent coronary angiogram within 6-months of T1-201 stress study, and (3) Studies were read blindly, and (4) Sensitivity and specificity were the endpoints of the studies. Articles involving patients with a history of coronary artery bypass graft surgery were excluded from this analysis. The submission included a total of 25 articles that met the above criterion, and further divided into two groups: those using IV Persantine (14) and those using IV Adenosine (11). A total of 1217 patients received IV Persantine, while 1397 patients received adenosine Thallium-201.

The objective of the meta-analysis was to combine the diagnostic sensitivities and specificities from multiple studies in order to arrive at a single estimate.

Statistical Methods: Separate meta-analysis was performed for studies using dipyridamole and adenosine stratified by two subgroups: severity of coronary stenosis as determined by angiography luminal area narrowing (≥70% versus ≥50%). DerSimonian and Laird's weighted method, a variance-based approach that incorporated the fixed and random effects linear models was employed to calculate the combined sensitivity and specificity. Both models are commonly used in the meta-analysis to account for sampling error and variability in the population effect size. A fixed effects model assumes constant true effect size (homogenous) for all studies, and the observed effect-size is the sum of the constant and within-study sampling error, whereas a random effects model assumes that the observed effect-size is heterogenous. Heterogeneity was tested by DerSimonian and Laird's Q-statistic, which is approximately distributed as Chi-square. A statistically significant heterogeneity implied that the variation in sensitivity and specificity between studies was significantly larger than expected by chance alone.

Results: Number of patients studied across studies ranged from 25 to 194 in the IV persantine

studies and 13 to 443 in the adenisone studies. The diagnostic sensitivity and specificity ranged from 83% to 95% and 48% to 100%, respectively across studies .

Table 1 shows the combined estimate of sensitivity and specificity by subgroup and overall using both fixed and random effects model. In both IV persantine and Adenisone Thallium studies, there were statistically significant heterogeneity ($p<0.05$) in the ≥50% stenosis subgroup relative to specificity. This is probably attributed to the small number of patients studied in the above subgroup. Although fixed effects model appeared to be more appropriate in the absence of heterogeneity, the sponsor's analyses included point estimates using both models and the results appeared consistently similar. The overall specificity for IV persantine group in Table 1 is a pooled estimate (reviewer's analysis), not an estimate from model. The Sponsor provided no specific reason for not being able to estimate specificity.

Table 1
Sensitivity and Specificity* (%) of IV Persantine and Adenosine Thallium by CAD Severity

Pharmacologic Stress	CAD Severity	Fixed Effects Model		Random Effects Model	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
IV Persantine	Stenosis: ≥70%	91 [89, 94] (n=694)	77 [71, 82] (n=219)	91 [88, 94] (n=694)	77 [71, 82] (n=219)
	≥50% - <70%	89 [85, 93] (n=227)	68 [58, 78] (n=77)	89 [85, 94] (n=227)	68 [50, 87] (n=77)
	Overall	**91 [89, 93] (n=921)**	**72 [67, 77)** (n=296)**	**90 [90, 93] (n=921)**	**72 [67, 77]** (n=296)**
Adenosine	Stenosis: ≥70%	93 [88, 98] (n=98)	100 [87, 100] (n=14)	93 [88, 98] (n=98)	100 [87, 100] (n=14)
	≥50% - <70%	89 [87, 91] (n=1046)	90 [86, 94] (n=239)	89 [86, 91] (n=1046)	88 [82, 95] (n=239)
	Overall	**89 [87, 91] (n=1144)**	**91 [87, 94] (n=253)**	**89 [87, 92] (n=1144)**	**90 [84, 95] (n=253)**

* Compiled from Sponsor's submission
** Pooled estimate

For both IV persantine or adenosine Thallium T-201 group, the overall diagnostic sensitivity is approximately 90% and there appeared to be no significant differences between the two CAD subgroups, with the lower bound of the 95% confidence interval exceeding 85% based on both statistical models. But the specificity differed between the two disease severity subgroups, more so for IV persantine studies than adenosine studies, with lower bound of 50% and >80%, respectively under fixed effects model. It appears that Persantine is less specific than adenisone Thallium in

intermediate stenotic (50-70%) patients with a lower bound that is comparable to the lower bound seen in NDA 19-817 and NDA 20-059.

3. Reviewer's Comment on the Sponsor's Analysis

1) Statistical methods (fixed and random effects model) used in the meta-analysis were acceptable.

2) Number of patients varied significantly across stress agents with respect to disease severity – higher percentages of severely stenotic (≥70%) patients were studied with IV persantine than adenisone Thallium (75% vs. 8%). This could have potentially induced selection or referral bias that may have impacted the efficacy estimates

3) Overall, in conjunction with Thallium T-201, the sensitivity of both IV persantine and Adenisone was approximately 90% regardless of disease severity, with a lower bound exceeding 85%. The specificity for both agents was also higher than the original clinical studies except for less stenotic Persantine subgroup (50% - 70%) where point estimates ranged from 68% to 100%, with a lower bound as low as 50%. This may be attributable to disease heterogeneity as noted above as indicated by the Q-statistic seen across studies.

4) Regardless of limitations of meta-analysis such as referral and publication bias (potential exclusion of negative studies) that are not accounted for in the statistical models, the sensitivity and specificity of both agents appeared to be higher than seen in the original clinical studies submitted in NDA 19-817 and NDA 20-059.

From statistical perspective, the sponsor's approach to the meta-analysis was reasonable but the robustness of this combined sensitivity and specificity is subject to the same criticism as in any other meta-analysis due to the reasons noted above. At best, this result could be seen as supportive, but not an alternative to efficacy generally shown in well-controlled trials.

Mahboob Sobhan, Ph.D.
Mathematical Statistician, HFD-715

Concur: Michael Welch, Ph.D., Team Leader, HFD-715

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/s/

Mahboob Sobhan
7/19/04 04:14:20 PM
BIOMETRICS

Mike Welch
7/20/04 10:30:14 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

ADMINISTRATIVE DOCUMENTS

13. Patent Information on any patent which claims the drug (21 U.S.C. 355(b) or (c))

Mallinckrodt, Inc. has examined the patent literature and declares that there are no unexpired patents that cover the formulation, composition, and/or method of use of Thallous Chloride Tl 201 Injection. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

Certified by:

James W Brodack Date 29 Sep 03

James W. Brodack Ph.D.
Manager Regulatory Affairs
Mallinckrodt, Inc.

14. Patent certifications with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)A))

Paragraph IV Certification

I, Mallinckrodt, Inc, certify that Patent Number 5,070,877 will not be infringed by the manufacture, use or sale of Thallous Chloride Tl-201 Injection for which this application is submitted.

Certified by:

Date 9/24/03

Tim A. Cheatham
Senior Patent Consul
Mallinckrodt, Inc.

Mallinckrodt, Inc. will comply with the requirements under 21 CFR 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 21 CFR 314.52(c) with respect to the content of the notice.

Paragraph II Certification

Mallinckrodt, Inc., in its opinion and to its best knowledge, certifies that Patent Number 3,993,538 has expired and therefore will not be infringed by the manufacture, use or sale of Thallous Chloride Tl-201 Injection for the use for which this application is submitted.

Certified by:

Date 9/24/03

Tim A. Cheatham
Senior Patent Consul
Mallinckrodt, Inc.

In its opinion and to its best knowledge, Mallinckrodt certifies that there are no additional patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

EXCLUSIVITY SUMMARY FOR NDA # __18-150__ SUPPL # ____SE 1___

Trade Name Thallous Chloride_T1-201 Generic Name _____

Applicant Name Mallinckrodt Inc. HFD # 160____

Approval Date If Known July 23,2004___

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_505(b)2_SE1__

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

YES /___/ NO /__X_/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

_____

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

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X _/ NO /___/

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

NDA# _ 18,110_ Thallium Chloride TL-201

NDA# __17,806 _Thallous Chloride, TL-201

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /X /

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

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

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

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

remainder of summary for that investigation.

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

_____

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

YES /___/ NO /___/

If yes, explain:

_____

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

_____

_____

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1 !

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

Investigation #2

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

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Diane C. Smith, R.Ph. Date November 15, 2004
Title: Regulatory Health Project Manager

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 05/10/2004

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/s/

Sally Loewke
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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 18-150 **Supplement Type (e.g. SE5):SE1** _____ **Supplement Number:** 019

Stamp Date: September 30, 2003 **Action Date:** July 23, 2004

HFD 160 **Trade and generic names/dosage form:**

Applicant: Mallinckrodt, Inc **Therapeutic Class:** 6S

Indication(s) previously approved:

Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging using either planar or SPECT (Single Photon Emission Computed Tomography) techniques for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the perfusion defect.

Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct to the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.

Thallous Chloride Tl 201 is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for postsurgical reexamination. Thallous Chloride Tl 201 has not been adequately demonstrated to be effective for the localization of normal parathyroid glands.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Thallous Chloride T1 201 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 and who cannot exercise adequately.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is mplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max 18 **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: The pharmacologic stress agents have not been approved for the pediatric population < 18 years of age.

Date studies are due (mm/dd/yy): Five years after the approval of any pharmacologic stress agents in pediatric patients._____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Diane C. Smith, R.Ph._____
Regulatory Project Manager

cc: NDA 18-150
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Diane Smith
7/21/04 01:06:32 PM

16. Debarment Certification (FD&C Act 306 (k)(1))

Mallinckrodt, Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Certified by:

James W Brodack . Date 29Sep03

James W. Brodack Ph.D.
Manager Regulatory Affairs
Mallinckrodt, Inc.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 18-150	Efficacy Supplement Type SE1-	Supplement Number 019
Drug: Thallous Chloride		Applicant: Mallinckrodt, Inc.
RPM: Diane C.Smith	HFD- 160	Phone # (301) 827-7510

Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(X)** Confirmed	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-817 IV Persantine® and NDA 20-059 Adenoscan®

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	6S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 30, 2004
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4611
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified (No form)
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (X) Verified (The sponsor has contacted the patent holders; SEE ACTION PACKAGE)
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	(X) Yes ( ) No ( ) Yes (X) No ( ) Yes (X) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes **(X)** No ( ) Yes **(X)** No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H N/A
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (Pending)
• Documentation of discussions and/or agreements relating to post-marketing commitments	X (Pending)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD/;MTL
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X July 19, 2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A X 9/24/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed N/A ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

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/s/

Diane Smith
7/21/04 01:17:56 PM

Division of Medical Imaging and Radiopharmaceutical Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: SE 019 FA, NDA 18-150

Name of Drug: Thallous Chloride T1 201

Applicant: Mallinckrodt Inc.

Material Reviewed:

Submission Date: January 28, 2005

Receipt Date(s): January 31, 2005

Background and Summary

The sponsor was sent an approval letter dated July 23, 2004, requesting final printed labeling.

Review

The sponsor has submitted final printed labeling identical to the labeling in the Action letter.

Conclusions

The final printed labeling is acceptable, and the sponsor will be sent an acknowledge and retain letter.

Diane C. Smith, R.Ph.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Kyong Kang, Pharm D.
Chief, Project Management Staff

Drafted: DCS/April 5, 2005
Revised/Initialed:
Finalized:
Filename: Document1

CSO LABELING REVIEW

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/s/

Diane Smith
4/5/05 04:28:15 PM
CSO

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS HFD-160

Internal Teleconference Meeting Minutes for NDA 18-150, SE1-019

PARTICIPANTS:

Virginia Beakes, Director, Division of Regulatory Policy II
Elaine Tseng, Regulatory Policy Analyst, Division of Regulatory Policy II
Raquel Peat, Regulatory Project Officer, Immediate Office, HFD-020
Zili Li, M.D., MPH, Clinical Team Leader, HFD-160
Diane C. Smith, R.Ph., Regulatory Health Project Manager, HFD-160

PURPOSE: This is a 505(b)(2) application and an internal meeting was held to discuss the use of other approved Thallous Chloride products that are used for stress testing, and to discuss the sponsor's question involving similar applications and the paying of a User Fee, once NDA 18-150 is approved.

DISCUSSION AND RECOMMENDATIONS: A summary of discussions and conclusions reached at the meeting are listed below:

1. The Project Manager indicated that the sponsor questioned in a recent teleconference as to whether other sponsor's submitted an NDA for their Thallous Chloride product, in addition, if the Agency would require the sponsor's to pay a User Fee. The Project Manager was advised to inform the sponsor to contact the User Fee Office for clarification on what fees would be required for applications for Thallous Chloride product(s).

2. A clarification was asked on other approved Thallous Chloride products used for imaging during stress testing, and the use with other pharmacologic agents. The Clinical Team Leader provided the following discussion points:
    - There are currently four commercially available FDA-approved Thallous Chloride Tl 201 (thallium), which are used as an imaging agent during the stress testing;
    - The sponsor of this particular thallium product is seeking a pharmacologic stress indication, in conjection with a pharmacologic agent (either IV Persantine or Adenoscan);
    - We have consulted the Division of Cardio-Renal and were told in writing that thallium, in conjunction with a pharmacologic stress agent (either IV Persantine or Adenoscan), have been found by that division to be safe and effective under NDA 19-817 (IV Persantine) and NDA

20-059 (Adenocan). But this indication only shows at IV Persantine and Adenoscan but not in thallium labeling;

- This Division found that the data used to support the Agency's prior decisions is still compatible with the current standards to approve similar imaging drugs for the same indication.
- Additional clinical data (literature review) presented by the sponsor did not cast any doubt on the performance of thallium as a pharmacologic stress imaging agent.

MINUTES PREPARER_____

LCDR Diane Smith, Pharm.D.
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

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/s/

Diane Smith
12/6/04 09:30:47 AM

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS HFD-160

Teleconference Meeting Minutes July 21, 2004

NDA: **18-150**

DRUG: **Thallous Chloride T1 201**

Sponsor: **Mallinckrodt, Inc.**

Date: **July 21, 2004**

FDA ATTENDEES:

Zili Li, M.D., Clinical Team Leader
Diane C. Smith, R.Ph., Regulatory Health Project Manager

SPONSOR ATTENDEES:

Dennis Nosco, Ph.D., Regulatory Affairs Associate
James W. Brodack, Ph.D., Regulatory Affairs Manager

AGENDA:

This is a brief teleconference requested by the Division to discuss the agreed upon labeling for NDA 18-150 Thallous Chloride T1 201, and the Pediatric study waiver request.

DISCUSSION:

The sponsor acknowledged receipt to the Division's proposed labeling and agreed to all of the proposed changes.
The sponsor was notified that the waiver of their Pediatric stud(s) could not be granted, but instead a deferral appeared to be the best option. The Division is willing to defer the required pediatric study until 5 years after the approval of any pharmacologic stress agents in the United States. The Division noted that such a deferral will be automatically considered as a phase 4 commitment under the Pediatric Research Equity Act (PREA). The sponsor agreed to the pediatric study deferral and the phase 4 commitment.

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/s/

Diane Smith
11/18/04 02:43:53 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 21, 2004

To: Dennis Nosco	**From:** Diane C. Smith
Company: Mallinckrodt Inc.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (314) 654-8905	**Fax number:** (301) 480-6036
Phone number: (314) 654-7255	**Phone number:** (301)827-7510

Subject: Enclosed is a draft of the proposed labeling for NDA 18-150 Thallous Chloride T1 201.

Total no. of pages including cover: 10

Comments: Please respond as soon as possible. Thank you, Diane C. Smith

Document to be mailed: • YES ☑ NO

8 page/s of draft labeling was/were removed from this portion of the review

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/s/

Diane Smith
7/21/04 11:25:02 AM
CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Review

NDA: 18-150

Sponsor: Mallinckrodt, Inc

Submission: Consult request (25 March 2004) seeks clarification of the Division's interpretation of data obtained using thallous chloride in the approvals for pharmacological stress agents, persantine and adenosine.

Review date: 6 May 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: Douglas C. Throckmorton, M.D., Director, HFD-110

The product label for IV Persantine (NDA 19-817; withdrawn) says, in part:

> *IV Persantine (dipyridimole USP) is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.*
>
> *In a study of about 1100 patients who underwent coronary arteriography and IV Persantine assisted thallium imaging, the results of both tests were interpreted blindly and the sensitivity and specificity of the Persantine thallium study in predicting the angiographic outcome were calculated. The sensitivity of the Persantine test (true positive Persantine divided by the total number of patients with positive angiography) was about 85%. The specificity (true negative divided by the number of patients with negative angiograms) was about 50%.*
>
> *In a subset of patients of patients who had exercise thallium imaging as well as Persantine thallium imaging, sensitivity and specificity of the two tests was (sic) almost identical.*

The product label for Adenoscan (NDA 20-059) says, in part:

> *In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (>/=50% reduction in the luminal diameter of at least one major vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiograms) was 54% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity were 37% to 71%.*

*Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (See **WARNINGS**).*

Mallinckrodt interprets the labels for dipyridimole and Adenoscan as making pharmacologic stress testing with thallium an approved indication, even though their label for thallous chloride is limited to use with exercise.

The Cardio-Renal Division Director's "approvable" memo of 9 November 1993 for Adenoscan says, in part:

> *Adenoscan (adenosine, by i.v. infusion over 6 minutes), like dipyridimole (which we have approved), is meant to be used as an adjunct to thallium scanning and because of the systemic effects of adenosine can be reasonably thought (for purposes of thallium scanning) to function as a surrogate for exercise. It is indeed not unusual for cardiologists to desire both a resting and an exercise thallium scan when considering the best strategies for therapy of patients with exercise induced chest pain. The rationale, pharmacology and physiology are complex, and I shall not summarize these concepts here. Suffice it to say that thallium, exercise thallium, dipyridimole-thallium, and adenosine-thallium (even without its being approved) are essentially part of what many would currently consider standard care.*
>
> *As was detailed in our considerations of dipyridimole (NDA 19-817), exercise testing (as evaluable from published studies) is pretty safe. It was our judgment that dipyridimole was less safe than exercise, but that for those who could not exercise, use of dipyridimole was a practical (and an only) alternative, when in a physician's judgment the results of the equivalent of an exercise thallium were required for appropriate patient care.*
>
> *For Adenoscan, the original NDA contained information for just those few minutes that immediately surrounded the thallium scan itself. Thus, the major deficiency was that delayed or persistent adverse events were not able to be evaluated. Additionally, hypotension seemed not to be well enough defined, as was also true for the appearance of arrhythmias. Lastly, and now perhaps the major issue, it was not clear that the adenosine-thallium test was sufficiently correlated with the results of angiograms, thus the purposes of doing the test were in some question.*

In the "non-approval" memo of 30 January 1995, Dr. Lipicky opines "that the value of coronary arteriography is not viewed in terms of its clinical outcome predictive value, but rather with respect to its utilitarian value at anatomical localization", which he called "beyond question". He proposes that is the standard by which Adenoscan should be judged.

Dr. Lipicky concluded, based on pooled data, that thallium-based exercise testing was not a very good diagnostic test, having a positive predictive value of about 0.96 but a negative predictive value of only about 0.12, compared with angiography. However, from two studies in which subjects received angiography, thallium with exercise, and thallium with Adenoscan, the results with Adenoscan and exercise are strikingly similar.

Thus the results of thallium imaging were used to confirm the efficacy of persantine and Adenoscan as pharmacologic stress agents. As part of the trials, the data were considered adequate to validate the use of thallium imaging plus pharmacologic stress

(with these agents) in identifying myocardial perfusion defects, as angiographic data were well correlated with the thallium imaging. Based on these studies, then, it seems reasonable to conclude that thallium imaging, employed in pharmacologic stress testing with persantine or Adenoscan, should be considered effective and adequately safe.

I see no evidence that the Division of Cardio-Renal Drug Products consulted with the division responsible for medical imaging at the time these products were being developed. Had that been done, it seems rather more likely that labeling among the three products would be consistent.

The Division of Cardio-Renal Drug Products would be happy to engage in further discussions on this issue.

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/s/

Norman Stockbridge
5/6/04 12:44:29 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-150 / S-019

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-150

Mallinckrodt, Inc.
Attention: Dennis Nosco, Ph. D
Regulatory Affairs Associate
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Dear Dr. Nosco:

We acknowledge receipt of your January 28, 2005 submission containing final printed labeling in response to our July 23, 2004, letter approving your new drug application (NDA) for Thallous Chloride T1 201 Injection.

We have reviewed the labeling that you submitted in accordance with our January 28, 2005 letter, and we find it acceptable.

If you have any questions, call Diane C. Smith, Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

George Q. Mills, 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

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/s/

Kyong Kang
4/11/05 12:36:51 PM
Signing for George Mills, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 18-150

FILING COMMUNICATION

Mallinckrodt, Inc.
Attention: Dr. James W. Brodack
675 McDonnell Bouvelard
P.O. Box 5840
St. Louis, MO 63134

Dear Dr. Brodack:

Please refer to your September 29, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thallous Chloride T1 201.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 28, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

- The literature may not be adequate based on our guidance to support the indication of pharmacologic stress for Thallous Chloride T1 201.
- The applicability of the Summary Basis of Approval for the referenced agents, IV Persantine® and Adenoscan®, to your Thallous Chloride T1 201 application.
- The current labeling is inadequate. The labeling must include revisions to the Clinical Studies and Adverse Reactions sections (include an adverse events table) in support of Thallous Chloride T1 201.
- The Adverse Events table should represent all events 0.5% and greater from all available data sources.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

- Please provide revised labeling to include a Clinical Studies and Adverse Reactions section.
- Please provide an Adverse Event table for all events 0.5% and greater from all available data sources.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Diane C. Smith, R.Ph, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Sally Loewke, M.D.,
Acting Division Director for the
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Sally Loewke
12/12/03 05:00:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-150

Mallinckrodt Inc.
Attention: James W. Brodack, Ph.D.,
Regulatory Affairs Manager
P.O. Box 5840
St. Louis, Missouri 63134

Dear Dr. Brodack,

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Thallous Chloride TI 201

Review Priority Classification: Standard

Date of Application: September 29, 2003

Date of Receipt: September 30, 2003

Our Reference Number: NDA 18-150

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 30, 2003, accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 30, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight :Mail:
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products-HFD-160
Attention: Division Document Room, 18B 45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane C. Smith, R.Ph., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Patricia Stewart
Acting Chief Project Manager
Division of Division of Medical Imaging
and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Patricia Stewart
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