CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-059/S-007

8/31/01

Fujisawa Healthcare, Inc.
Attention: Mr. Donald R. Peckels
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Dear Mr. Peckels:

Please refer to your supplemental new drug application dated July 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adenoscan (adenosine) 3 mg/ml Injection.

We acknowledge receipt of your submission dated January 16, 2001. Your submission of January 16, 2001 constituted a complete response to our July 31, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. Under **PRECAUTIONS/Drug Interactions**, the word "alkylxanthines" has been changed to "methylxanthines" in the first sentence of the second paragraph.

2. Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the second paragraph has been changed to:

   > Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

3. Under **PRECAUTIONS**, the proposed **Geriatric Use** subsection has been changed to read as follows:

   > Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

4. The word "injection" has been added after the word "adenosine" throughout the package insert. Please make this corresponding change in the carton/container labeling at the time of your next printing. This change should reported in your annual report.

5. Under **HOW SUPPLIED**, the statement: **"CAUTION**: Federal law prohibits dispensing without prescription." has been replaced with **"Rx only."**

We have completed the review of this supplemental 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 final printed package insert included in your January 16, 2001 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

6Sincerely, /S/

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Raymond Lipicky
8/31/01 12:22:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Final Printed Labeling

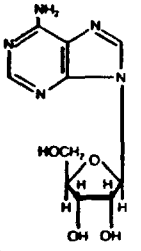
Fujisawa

ADENOSCAN®

adenosine injection

For Intravenous Infusion Only

DESCRIPTION:
Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine and has the following structural formula:



$C_{10}H_{13}N_5O_4$ 267.24

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

CLINICAL PHARMACOLOGY:
Mechanism of Action
Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A_1 and A_2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A_2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since Adenoscan significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Adenoscan causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e., a greater difference is seen after Adenoscan between areas served by normal and areas served by stenotic vessels than is seen prior to Adenoscan.

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%.

Intracoronary Doppler flow catheter studies have demonstrated that a dose of intravenous Adenoscan of 140 mcg/kg/min produces maximum coronary hyperemia (relative to intracoronary papaverine) in approximately 95% of cases within two to three minutes of the onset of the infusion. Coronary blood flow velocity returns to basal levels within one to two minutes of discontinuing the Adenoscan infusion.

INDICATIONS AND USAGE:
Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (See WARNINGS)

CONTRAINDICATIONS:
Intravenous Adenoscan (adenosine injection) should not be administered to individuals with:
1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS:
Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction.
Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and non-fatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block
Adenoscan (adenosine injection) exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hemodynamics

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A_1-receptor agonism, and produces peripheral vasodilation, presumably due to A_2-receptor agonism. The net effect of Adenoscan in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Pharmacokinetics

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m and V_{max} than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As Adenoscan requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

Clinical Trials

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

Hypotension

Adenoscan (adenosine injection) is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenoscan (adenosine injection) is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS:

Drug Interactions

Intravenous Adenoscan (adenosine injection) has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however,

Adenoscan should be used with caution in the presence of these agents.

The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated.

The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated.

Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan (adenosine injection). Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.

Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

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.

OVERDOSAGE:

The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION:

For intravenous infusion only.

Adenoscan should be given as a continuous peripheral intravenous infusion.

The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg).

The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan). Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set.

The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered.

There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.

The safety and efficacy of Adenoscan administered by the intracoronary route have not been established.

The following Adenoscan infusion nomogram may be used to determine the appropriate infusion rate corrected for total body weight:

Patient Weight		*Infusion Rate*
kg	*lbs*	*mL/min*
45	99	2.1
50	110	2.3
55	121	2.6
60	132	2.8
65	143	3.0
70	154	3.3
75	165	3.5
80	176	3.8
85	187	4.0
90	198	4.2

This nomogram was derived from the following general formula:

$$\frac{0.140\ (\text{mg/kg/min}) \times \text{total body weight (kg)}}{\text{Adenoscan concentration (3 mg/mL)}} = \text{infusion rate (mL/min)}$$

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED:

Adenoscan (adenosine injection) is supplied as 20 mL and 30 mL vials of sterile, nonpyrogenic solution in normal saline.

Product Code	NDC No.	
87120	0469-0871-20	60 mg/20 mL (3 mg/mL) in a 20 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.
87130	0469-0871-30	90 mg/30 mL (3 mg/mL) in a 30 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.

Store at controlled room temperature 15°-30°C (59°-86°F).

Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

Contains no preservative. Discard unused portion.

Rx only

Manufactured for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015

58-6295-R3
Revised: September 2000

Fujisawa

58-6295-R3-Revised: September 2000

ADENOSCAN®

adenosine injection

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-059/S-007

JUL 31 2000

Fujisawa Healthcare, Inc.
Attention: Laurence R. Meyerson, Ph.D.
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Dear Dr. Meyerson:

Please refer to your supplemental new drug application dated July 28, 1999, received August 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adenoscan (adenosine) Injection, 3 mg/ml.

We acknowledge receipt of your submission dated May 25, 2000.

This supplemental new drug application proposes changes in the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection and also the establishment of a **Geriatric Use** subsection under **PRECAUTIONS**.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. The word "alkylxanthines" has been changed to "methylxanthines" throughout the package insert.

2. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, the second paragraph has been changed to:

   Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

3. Please revise your proposed **PRECAUTIONS: Geriatric Use** subsection to read as follows:

   Clinical studies of Adenoscan did not include sufficient number of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

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

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

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

/S/ 7/31/00

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-059
HFD-110/Div. Files
HFD-110/E.Fromm
HFD-002/ORM
HFD-101/ADRA
HFD-42/DDMAC ~~(with labeling)~~
DISTRICT OFFICE

/S/ 7-31-00

Drafted by: ef/July 24, 2000
Initialed by: K Srinivasachar/7/25/00
T Papoian/7/25/00
A DeFelice/7/25/00
S Rodin/7/31/00
A Karkowsky/7/31/00
Z McDonald/7/31/00
Final: asb/7/31/00
Filename: 20-059s007(ae).doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Medical Review(s)

JUN 1 2 2000

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 12. 2000

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-Renal Drug Products HFD-110

SUBJECT: Geriatric labeling for adenosine (Adenoscan ®) infusion (NDA 20-059)

Dr. Rodin's reviews contains information on safety from 11 literature citations. Three of these citations[1, 2, 3] contain some specific information on the use of Adenoscan in the elderly. The definition of elderly in each of the papers and the number of such patient s enrolled is shown in Table 1.

Study	Definition of Elderly	Number of elderly	Comments
Hashimoto et al.;[1]	Patients > 75 years	101 with adenosine 116 with adenosine plus exercise	Not randomized.
Cergueira et al.;[2]	>65	approximately 5090	Not randomized
Johnston et al.;[3]	> 70 years	997	Not randomized

None of these publications either alone or in combination are adequate to determine that Adenoscan is a useful adjunct to the management or the decision making process in the elderly.

The relative safety of the cohort of patients defined as elderly in each of the study was qualitatively he same as those less senior. Quantitatively, the incidence of AV block was increased in the elderly versus less senior (17.8% versus 7.9% among those with Adenoscan and 13.0% versus 3.2 % among those with Adenoscan plus exercise). The degree, intensity and reversibility of this A-V block were not stated In this study the elderly were more likely discontinued prematurely from the infusion (14.9 % versus 7.9% for those with Adenoscan and 5.3% versus 3.8% for those with exercise and Adenoscan)[1]. In a second study[2], age (> 70) was an independent predictor of A-V blockade

Consequently, some modification of the standard geriatric labeling appears reasonable.

> *"Clinical studies of Adenoscan did not include sufficient number of subjects aged 65 years old and over to determine whether they respond differently from younger subjects. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out."*

---

[1] Hashimoto, A.; Palmer, El; Scott, JA; Abraham SA; Fischman,AJ; Force, TL; Newell, JB; Rabito, CA; Zervos, GD; and Yasuda, T; 1999; J Nucl Cardiol. 6: 612-9. "Complication of Exercise and Pharmacologic Stress Tests: Differences in Younger and Elderly Patients".

[2] Cerqueira, MD; Verani, MS; Schwaiger, M; Heo, J; and Iskandrian, AS. J Amer Coll Cardio. 1994; 23: 384-9. "Safety Profile of Adenosine Stress Perfusion Imaging: Results From Adenoscan Multicenter Trial Registry"

[3] Johnston, DL; Hodge, DO; Hopfenspringer, MR; Gibbons, RJ Mayo Clin Proc; 1998 73: 314-320 " Clinical Determinants of Hemodynamic and Symptomatic Response in 2,000 Patients During Adenosine Scintigraphy."

cc: NDA 20-059 submission 7/28/99 and 8/6/99; Akarkowsky/Srodin/CSO

amended

JUN 5 2000

U.S. PUBLIC HEALTH SERVICE

Steven Mark Rodin, M.D.
Medical Officer

Food Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

ADDENDUM to Medical Review of Geriatric labelling supplement

date:	6/5/2000
NDA #:	20-059 ; submission 7/28/99, 8/6/99
Drug:	Adenosine (Adenoscan®, Fijusawa Healthcare)

Since my prior review of 5/25/200 one additional relevant publication was submitted (by fax) by the sponsor. This work by Hashimoto et. al[1]. described, in addition to treatment groups not relevant to the present considerations, a group of 354 patients referred for diagnostic testing and exposed to adenosine 0.14 mg/kg/min for 5 minutes without concomitant exercise exertion. Of these, 253 were ≤75 years and 101 were 75 years.

There were reportedly no significant hemodynamic differences at baseline, but the pre-treatment balance of age and cardiac risk factors is not clear. In a non-blinded assessment of adverse events the mean rate of atrioventricular (AV) block during adenosine exposure was higher in the older age group (17.8 vs 7.9%, respectively). Reportedly all AV block episodes ceased withing several seconds of adenosine discontinuation. During adenosine exposure directionally similar (although quantitatively smaller) age-related trends were noted for sinus bradycardia (6.9 vs 4.3%, respectively), angina (15.8 vs 13.4%, respectively), and flushing (9.9 vs 4.0%, respectively).

Revised Recommendation:

Although the nature of the submitted data limits the conclusiveness of inferences about geriatric use, given the agreement of the Cerqueria evidence (discussed in my review of 5/25/200) and these present Hashimoto data, I would strengthen the language of my prior labelling recommendation to include mention that elderly patients may be more vulnerable to adenosine-induced AV block.

/S/ MD 6/5/00

Steven Mark Rodin, M.D. Date

1 attachment
cc: HFD-110/ division file, CSO, A.Karkowsky, *no copy to S.Rodin

[1] J Nucl Cardiol 1999; 6:612-9.

Attachment: photocopy of Hashimoto et. al.; J Nucl Cardiol 1999; 6:612-9.

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 ∃ Telefax (847) 317-7286 (Regulatory Affairs)

Fujisawa

FACSIMILE

DATE: May 25, 2000

FAX NO: 301-594-5379

TO: Dr. Steve Rodin

FROM: Don Peckels

CC:

SUBJECT: Adenoscan (adenosine injection)
NDA 20-059 / S-007

PAGES: 10

Dear Steve:

This is in reference to our teleconference meeting with Ms Denice Simons and Dr. Shri Gadgil, on the subject sNDA. Appended is a copy of the following additional literature article which Fujisawa Healthcare, Inc. (FHI) feels is relevant in support of the Geriatric Use subsection of Adenoscan labeling, proposed in the original submission of the subject sNDA:

> Hashimoto A, et. al., Complications of Exercise and Pharmacologic Stress Tests: Differences in Younger and Elderly Patients, J. Nucl. Card., 6:6; 612-619, Nov./Dec., 1999

As we discussed, FHI would appreciate it if you would consider the information in this article in your review of this sNDA.

I am also appending to this facsimile a copy of the proposed Geriatric Use labeling subsection for Adenoscan as it was proposed in the original supplement S-007 to NDA 20-059. As we stated in our teleconference, FHI is not proposing to make any changes to the proposed wording to this labeling subsection.

I will also forward a copy of this facsimile to you via overnight courier. I look forward to hearing from the Division on this matter. Please contact me at (847) 317-1587 if you have any questions.

Sincerely,

D R Peckels

Donald R. Peckels
Associate Director, Regulatory Affairs

Complications of exercise and pharmacologic stress tests: Differences in younger and elderly patients

Akiyoshi Hashimoto, MD,[a] Edwin L. Palmer, MD,[a] James A. Scott, MD,[a] Stephen A. Abraham, MD,[b] Alan J. Fischman, MD, PhD,[a] Thomas L. Force, MD,[b] John B. Newell, AB,[b] Carlos A. Rabito, MD,[a] Gerasimos D. Zervos, MD,[b] and Tsunehiro Yasuda, MD[a,b]

Background. Age characteristics of patients undergoing various types of stress tests are important because of differences in clinical background and exercise performance between the young and elderly. Adverse effects of pharmacologic agents are known to be more common in the elderly, who are less able to perform vigorous exercise stress testing. We investigated the clinical background, performance characteristics, and complication rate of various stress tests in younger (≤75 years old) and elderly (>75 years old) patient populations.

Methods. A total of 3412 patients (2796 younger, 616 elderly) underwent 5 types of stress tests with (1) technetium-99m sestamibi (MIBI) single photon emission computed tomography: symptom-limited exercise (Ex, 1598 younger, 173 elderly), (2) dipyridamole infusion (0.14 mg/kg/min, 4 minutes) without exercise (D, 260 younger, 114 elderly), (3) with exercise (DEx, 339 younger, 112 elderly), (4) adenosine infusion (0.14 mg/kg/min, 5 minutes) without exercise (A, 253 younger, 101 elderly), and (5) with exercise (AEx, 346 younger, 116 elderly).

Results. Sixty-seven percent of patients in the younger population were able to achieve 85% of the maximum predicted heart rate, whereas 54% of the elderly reached this level of exercise. No patient had life-threatening complications. In both the younger and elderly groups, chest discomfort, feelings of impending syncope, flushing, and fall in blood pressure occurred less frequently in DEx than D and in AEx than A. Sinus bradycardia occurred less frequently in AEx than A in the younger (1.2% vs 4.3%, $P < .05$) and elderly groups (0.9% vs 6.9%, $P < .05$). Atrioventricular block was less frequent in AEx than A in the younger group (3.2% vs 7.9%, $P < .05$) but not so in the elderly group (13.0% vs 17.8%, not significant). The frequency of ischemic electrocardiographic changes in DEx and AEx was very similar to that of Ex in both the younger and elderly groups, although ischemic electrocardiographic changes in D and A are known to be less frequent.

Conclusion. Of the elderly group who were judged to be fit to exercise to 85% of maximum predicted heart rate, nearly half failed to reach this level. In contrast, the younger patients were able to achieve this level in 67% of tests. Supplementation with modest exercise reduced most of the pharmacologically related adverse effects. The elderly group was not protected from atrioventricular block as effectively as the younger group by additional exercise in the adenosine stress test. Ischemic electrocardiographic changes in the pharmacologic stress test were as frequent as in the exercise stress test when modest supplementary exercise was added to the pharmacologic protocol. There were no deaths, myocardial infarction, or other major complications. These observations suggest that exercise and pharmacologic stress tests are safe in the elderly, including those patients more than 75 years old. (J Nucl Cardiol 1999;6:612-9.)

Key Words: Exercise stress test • adenosine • dipyridamole • adverse effect • complication of stress test

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Exercise stress testing with myocardial perfusion imaging provides important clinical information including location of ischemia, risk assessment in coronary artery disease (CAD), and functional capacity.[1,2] Findings obtained from exercise are valuable for the treatment of patients of any age with or without known CAD. Poor exercise performance, however, may reduce the sensitivity of stress testing for identifying CAD.[1,2]

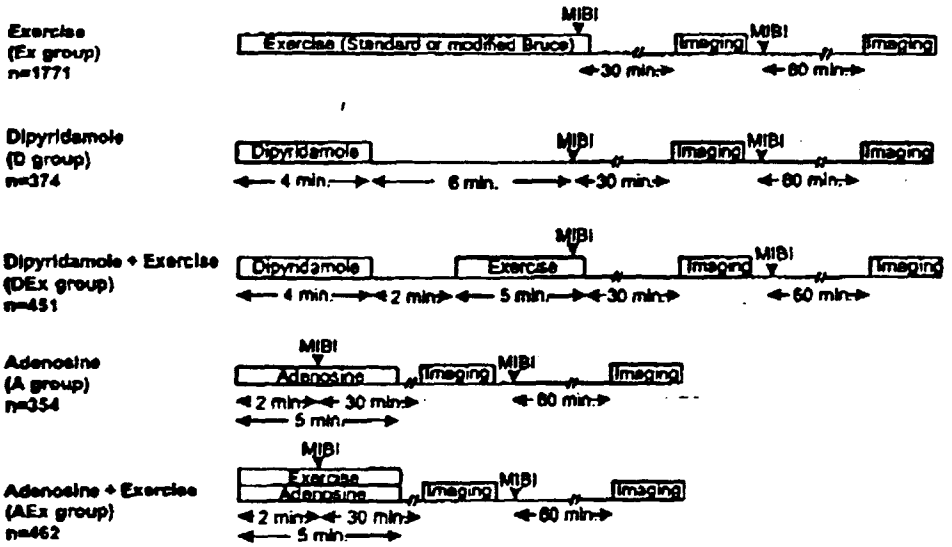

Figure 1. Eight mCi of sestamibi was injected 1 minute before completion of exercise in Ex and DEx groups. 6 minutes after the end of dipyridamole infusion in D group, or 2 minutes into the infusion of adenosine in A and AEx groups. Stress image acquisition was started 30 minutes after the initial injection of sestamibi, and rest imaging was performed 60 minutes after the subsequent injection of 24 mCi of sestamibi. Fifty milligrams of intravenous aminophylline was routinely administered after completion of stress imaging in D and DEx groups.

Pharmacologic coronary vasodilatation has been widely used for patients who are unable to exercise.[3] The elderly are likely to be principal candidates for a pharmacologic stress test because of limited ability to exercise. Unfortunately, adverse drug reactions are known to be more common in the elderly.[4] Once an adverse drug reaction occurs, the elderly patient's ability to recover may be impaired by reduced physiological compensatory function.[5] The clinical backgrounds, performance on various stress tests, and complication rate may differ between elderly and younger populations. This study was undertaken to quantify differences in terms of (1) clinical background, (2) exercise capacity and hemodynamic change, and (3) complications in younger and elderly patients undergoing 5 different types of stress tests.

METHODS

Patient Population

The study population consisted of 3412 patients: 2056 men and 1356 women with a mean age of 63.8 ± 12.6 years (range, 17 to 96 years). These included 2695 consecutive patients who were studied between January 1996 and November 1996. Fifty-two percent (1771) of the patients underwent symptom-limited treadmill exercise stress tests (Ex group), and 48% (1641) underwent pharmacologic stress tests. Patients referred for dipyridamole (D) with (n = 370) and without (n = 347) exercise between May 1994 and January 1996 were added to this population because of the extremely small number in the initial D and DEx groups. All patients underwent stress testing with sestamibi imaging for the purpose of diagnosing CAD, evaluating the extent and location of ischemia, follow-up after revascularization, preoperative evaluation, or

Table 1. Clinical characteristics

	Younger (n = 2796)	Elderly (n = 616)
Male (%)	63.3	46.3*
Coronary risk factors (%)		
Family history	42.3	26.3*
Smoking	17.3	9.3*
Diabetes mellitus	16.0	21.8*
Hyperlipidemia	41.7	24.0*
Hypertension	43.3	54.4*
History (%)		
Myocardial infarction	28.1	31.8
PTCA	12.5	9.7
Coronary artery bypass graft	11.4	12.0
Medication (%)		
Digitalis	10.8	13.5
Calcium channel blockers	19.1	23.5*
β-Blockers	37.5	41.6
Nitrates	20.6	25.3*
ACE inhibitors	17.5	19.5
Bronchodilators	1.6	0.8

PTCA, Percutaneous transluminal coronary angioplasty; *ACE*, angiotensin converting enzyme.
* $P < .05$ vs younger.

Table 2. Hemodynamic changes and exercise performance in the younger and elderly patients

	Exercise		Dipyridamole			
	Ex		D		DEx	
	Baseline	Peak	Baseline	Peak	Baseline	Peak
Younger	n = 1598		n = 260		n = 339	
HR(bpm)	72 ± 13	140 ± 28*	72 ± 15	89 ± 21*	71+13	105 ± 21*
SBP (mm Hg)	131 ± 20	166 ± 26*	134 ± 21	134 ± 26	135 ± 21	145 ± 29*
RPP (x1000)	9.4 ± 2.3	23.5 ± 6.3*	9.6 ± 2.5	12.1 ± 4.3*	9.4 ± 2.1	15.4 ± 5.0*
Exercise duration	7.8 ± 3.5		—		4.3 ± 1.3	
METs	9.4 ± 4.4		—		—	
Achieving 85% of MPHR‡	66.5%		—		—	
Elderly	n = 173		n = 114		n = 112	
HR(bpm)	70 ± 13	118 ± 27*	68 ± 12	82 ± 15*	67 ± 12	95 ± 19*
SBP (mm Hg)	139 ± 23	158 ± 26*	144 ± 25	139 ± 27†	141 ± 20	144 ± 26
RPP (x1000)	9.8 ± 2.5	19.4 ± 6.1*	9.8 ± 2.5	11.4 ± 3.2*	9.5 ± 2.1	14.0 ± 1.3*
Exercise duration	4.5 ± 2.2‡		—		4.0 ± 1.3	
METs	6.2 ± 2.4‡		—		—	
Achieving 85% of MPHR§	53.9%§		—		—	

HR, Heart rate; *SBP*, systolic blood pressure; *RPP*, rate pressure product; *MPHR*, maximum predicted heart rate.
*$P < .01$, baseline < peak.
†$P < .01$, baseline > peak.
‡$P < .05$ vs younger.
§This value was evaluated in 1557 patients who underwent standard Bruce protocol.

screening for CAD in a high-risk population. Patients who had contraindications such as significant high systolic blood pressure (>180 mm Hg) or diastolic blood pressure >100 mm Hg at rest), low systolic blood pressure (<90 mm Hg), severe aortic stenosis, severe mitral stenosis, high degree of atrioventricular block, or acute myocardial infarction were excluded from this study. Patients receiving bronchodilators (nontheophylline derivatives) were not excluded from adenosine or dipyridamole, unless they had had a recent (<7 days) acute asthma attack, severe respiratory failure treated with respirator, or wheezing at the time of physical examination before the stress test was performed.

Patients >75 years were defined as "elderly," and patients ≤75 years of age were defined as "younger."[6,7] Out of 1771 patients who underwent exercise stress tests, 1598 were ≤75 years of age (median age 59 years), and the remaining 173 were >75 years of age (median age 79 years). Pharmacologic stress tests were performed on 1641 patients who were unable to exercise adequately or were not expected to reach 85% of maximum predicted heart rate (MPHR). Each pharmacologic group was further divided into younger and elderly groups. The D stress tests without exercise included 260 younger patients (median age, 66 years) and 114 elderly patients (median age, 81 years). The D stress tests with exercise included 339 younger patients (median age, 64 years) and 112 elderly patients (median age, 80 years). The adenosine (A) stress tests without exercise included 253 younger patients (median age, 65 years) and 101 elderly patients (median age, 81 years). The A stress tests with exercise included 346 younger patients (median age, 65 years) and 116 elderly patients (median age, 80 years). Consequently, all 3412 patients were divided into the 2796 (82%) younger and the 616 (18%) elderly in this study.

Study Protocol

All patients were given intravenous injections of 8 mCi (296 MBq) sestamibi during peak exercise or pharmacologic stress and 24 mCi (888 MBq) at rest after the stress imaging (Figure 1). The decision whether to continue or discontinue daily medications was made by the referring physician.

Exercise Stress Test Protocol

Patients underwent symptom-limited treadmill exercise with the standard or modified Bruce protocol (Figure 1). The criteria for premature termination of exercise were (1) general fatigue, (2) feeling of impending syncope, (3) claudication or leg fatigue, (4) dyspnea, (5) severe angina pectoris, (6) ST segment horizontal or downsloping depression of 0.3 mV or greater accompanied by symptoms, (7) sudden onset of bradycardia, rhythm change, or high degree of atrioventricular block causing deterioration of vital signs, or (8) a fall in systolic blood pressure of more then 15 mm Hg.

Dipyridamole Stress Test Protocol

Intravenous dipyridamole was infused at 0.14 mg/kg/min for 4 minutes (Figure 1). Sestamibi was injected at the tenth minute

Adenosine			
A		AEx	
Baseline	Peak	Baseline	Peak
n = 253		n = 346	
72 ± 16	91 ± 20*	72 ± 14	101 ± 21*
133 ± 22	130 ± 25	134 ± 20	142 ± 26*
9.6 ± 2.5	11.8 ± 3.7	9.6 ± 2.4	14.5 ± 4.5*
	—		4.6 ± 1.4
	—		—
	—		—
n = 101		n = 116	
68 ± 12	84 ± 17*	71 ± 13	98 ± 19*
140 ± 23	133 ± 24†	142 ± 22	139 ± 25
9.6 ± 2.1	11.2 ± 3.5*	10.0 ± 2.0	13.6 ± 3.8*
	—		4.2 ± 1.4
	—		—
	—		—

in the D group. The DEx group was exercised for 5 minutes (1.7 mph, 0% grade) after the dipyridamole infusion was completed, and sestamibi was injected 1 minute before exercise was completed. Vital signs and electrocardiography were recorded every minute. Fifty milligrams of intravenous aminophylline was routinely administered 5 minutes after the sestamibi injection.

Adenosine Stress Test Protocol

In group A adenosine was infused intravenously without exercise at a rate of 0.14 mg/kg/min for 2 minutes before tracer injection. At that point sestamibi was injected, and the adenosine infusion continued for an additional 3 minutes, for a total of 5 minutes (Figure 1). In group AEx low-level exercise (0.5 to 1.7 mph, 0% grade) was simultaneously performed throughout the adenosine infusion period. The speed of exercise was adjusted so that patients in the AEx group were likely to complete 5 minutes of exercise. These protocols were based on the observation that the average time from the onset of adenosine infusion until the maximal increase in coronary blood flow is less than 90 seconds.[8] A 12-lead electrocardiogram was continuously monitored, and blood pressure was recorded every minute.

Assessment of Adverse Effects

All patients were asked whether they had any symptoms during or after a stress test. Chest pain was classified as either classical anginal or chest discomfort. Other symptoms such as wheezing, nausea, feelings of impending syncope, flushing, and headache were also recorded.

In an exercise stress test a fall in systolic blood pressure of 15 mm Hg or more after a second confirming measurement terminated the test. In most cases the patient had symptoms. During pharmacologic stress testing the blood pressure often varied widely, making clear definition difficult. However, for patients with normal baseline blood pressure, a drop in systolic blood pressure to below 100 mm Hg prompted a decision by the supervising clinician. A fall to below 90 mm Hg terminated the study. In patients with a baseline systolic blood pressure of 90 to 99 mm Hg, a fall to less than 90 mm Hg terminated the procedure even if the patient appeared to have no symptoms. Patients whose baseline systolic blood pressure was below 90 mm Hg were not considered for a stress test. In all cases the decision of whether to terminate a pharmacologic stress test because of a fall in blood pressure was made by the supervising clinicians.

Atrioventricular block of second degree or higher grade, sinus bradycardia of less than 40 bpm, or ventricular tachycardia defined as 3 or more consecutive ventricular premature contractions were identified by continuous electrocardiographic monitoring.

Analysis of Ischemic Electrocardiographic Changes

Ischemic changes were defined as horizontal or downsloping ST-segment depression of 1 mm or greater or ST-segment elevation of 1 mm or greater from normal baseline electrocardiography in more than 2 leads of the same region. If patients reached 85% of MPHR, and the electrocardiogram did not meet the positive criteria, the result was interpreted as negative for ischemia. If a patient could not achieve 85% of MPHR and did not have electrocardiographic changes, the ECG was read as nondiagnostic. The presence of nonspecific ST-T changes, left bundle branch block, right bundle branch block, intraventricular conduction defects, left ventricular hypertrophy, pacemaker rhythm, or Wolff-Parkinson-White syndrome were read as nondiagnostic for ischemia regardless of the exercise level achieved. Patients receiving digitalis were also placed in the nondiagnostic category.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Age is expressed as a median because of the arbitrary selection of 75 years as the border between young and elderly. Clinical characteristics were compared between groups with chi-squared analysis (Table 1). Changes in hemodynamic parameters during each stress test were evaluated by the paired t test (Table 2). Hemodynamic parameters among the 5 groups were compared by analysis of variance with Bonferroni corrected t tests. Comparison of differences in adverse effects among the 5 groups was examined by 2×5 chi-squared analysis. If a significant difference was found among the 5 groups, the incidence of the adverse effects was compared between 2 groups with 2×2 chi-squared analysis (Table 3). A probability value of $P < .05$ was considered significant.

Table 3. Adverse effects and stress test results

	Exercise		Dipyridamole				Adenosine			
	Younger	Elderly	Younger		Elderly		Younger		Elderly	
	n = 1598	n = 173	D n = 260	DEx n = 339	D n = 114	DEx n = 112	A n = 253	AEx n = 346	A n = 101	AEx n = 116
Patient symptoms (%)										
Anginal chest pain	16.5	15.6	11.9	17.2	15.8	18.8	13.4	17.3	15.8	16.5
Chest discomfort	3.5	4.0	10.0	5.3*	11.4	3.6*	22.5	7.2†	21.8	7.8
Flushing	0.0	0.0	3.1	0.6*	7.0	0.9*	4.0	1.2*	9.9	1.7*
Feelings of impending syncope	0.1	0.0	2.3	0.9	3.5	2.7	4.3	1.7*	8.9	1.7*
Wheezing	1.7	7.5	3.5	3.8	4.4	7.1	5.9	3.2	5.9	5.2
Headache	0.8	2.3	0.4	0.9	1.8	0.9	0.8	0.3	1.0	0.9
Nausea	0.4	1.7	1.9	0.3	1.8	0.0	1.6	1.4	2.0	0.9
Cardiac side effects (%)										
Fall in blood pressure	1.9	2.9	9.2	4.4*	11.4	3.6*	12.3	4.0†	12.9	4.3*
Sinus bradycardia	0.1	0.0	0.0	0.3	0.0	1.8	4.3	1.2*	6.9	0.9*
Atrioventricular block	0.6	1.2	0.0	0.6	0.0	1.8	7.9	3.2*	17.8	13.0
Ventricular tachycardia	1.5	1.2	1.2	0.3	0.9	0.0	0.8	0.3	1.0	0.0
Premature termination of infusion (%)	—	—	0.8	0.6	1.8	0.9	7.9	3.8*	14.9	5.3*
Stress test results (%)										
Ischemic electrocardiographic changes	12.8	9.8	5.0	11.2*	4.4	14.3*	4.0	12.1†	4.0	13.0*
Abnormal Scan										
Fixed	9.7	11.0	10.4	8.6	12.3	8.9	13.0	9.8	11.9	7.0
Reversible	29.7	33.5	35.8	35.1	33.3	34.0	31.7	35.3	36.6	39.1

*$P < .05$ vs without exercise (D or A).
†$P < .001$ vs without exercise (D or A).

RESULTS

Patient Characteristics

Comparison of the clinical backgrounds of younger and elderly patients is presented in Table 1. The proportion of men was significantly lower in the elderly group than in the younger (46.3% vs 63.3%, $P < .001$). Coronary risk factors were significantly different between the 2 groups. The proportion of patients referred for exercise stress test in the elderly group was much less (9.8%, 173 of 1771) compared with that in the younger group (90.2%, 1598 of 1771). No significant differences were seen in these baseline characteristics among the 5 groups within the younger or elderly patient populations.

Hemodynamic Changes

The hemodynamic responses of both patient populations are presented in Table 2. All 5 groups demonstrated significant increases in heart rate for both younger and elderly patients. In the younger groups a significant increase in systolic blood pressure was found in the Ex, DEx, and AEx groups. The elderly demonstrated significant increases in systolic blood pressure only in the Ex group. A significant decrease in systolic blood pressure was seen in the elderly D and A groups but not in the younger D and A groups.

No significant differences were found in baseline hemodynamic parameters among the 5 groups within either the younger or elderly populations. The younger and elderly Ex groups showed significantly greater peak heart rate, peak systolic blood pressure, and peak rate pressure product than did the pharmacologic groups. These hemodynamic parameters were significantly greater in the DEx and AEx compared with the nonexercise groups (D, A) in both the younger and elderly populations.

The duration of exercise was significantly longer in the younger Ex group compared with the elderly Ex group (7.8 ± 3.5 min vs 4.5 ± 2.2 min, $P < .001$). The

younger Ex group achieved a significantly higher level of metabolic equivalents than the elderly Ex group (9.4 ± 4.4 vs 6.2 ± 2.4, $P < .001$). In a subgroup excluding the modified Bruce protocol, the proportion of patients who achieved 85% of MPHR was significantly higher in the younger than in the elderly group (66.5% vs 53.9%, $P < .01$).

Adverse Effects

Characteristics of complications were analyzed separately in the younger and the elderly groups because of significant differences in clinical backgrounds. No patient in either group died or had a myocardial infarction or ventricular fibrillation. The incidence of adverse effects is shown in Table 3. Notably, supplementary exercise decreased the incidence of falling blood pressure, chest discomfort, flushing, and impending syncope in both the young and the elderly groups.

A significantly higher incidence of atrioventricular block or sinus bradycardia was observed in the A and AEx groups than with the Ex, D, or DEx groups for both younger and elderly patients. Sinus bradycardia occurred significantly less frequently in the AEx group than the A group in the younger (1.2% vs 4.3%, $P < .05$) and elderly (0.9% vs 6.9%, $P < .05$) groups. In all patients referred for adenosine stress test, the incidence of atrioventricular block was 7.8% (the A group 10.7%, the AEx group 5.6%). The incidence of atrioventricular block was significantly lower in the AEx group than in the A group in younger patients (3.2% vs 7.9%, $P < .05$). However, in the elderly patients no significant difference in the incidence of atrioventricular block was demonstrated between the AEx and A groups (13.0% vs 17.8%, P = not significant). Thus the incidence of atrioventricular block observed during adenosine infusion was not significantly reduced by supplementary exercise in the elderly patients. All episodes of atrioventricular block disappeared within several seconds of the discontinuation of the adenosine infusion. Only 6 of 64 patients who had second-degree atrioventricular block had transient complete atrioventricular block. Adenosine-induced atrioventricular block caused premature termination of the infusion in 13 patients (6 younger, 7 elderly) including 10 patients who had symptoms caused by atrioventricular block (ie, feelings of impending syncope).

Premature termination of dipyridamole or adenosine infusion was a consequence of impending syncope (30%), wheezing (20%), atrioventricular block (20%), a fall in blood pressure (16%), sinus bradycardia (7%), nausea (5%), and severe chest pain (2%). The incidence of the premature termination of the infusion was significantly lower in the AEx group than in the A group in younger (3.8% vs 7.9%, $P < .05$) and elderly patients (5.3% vs 14.9%, $P < .05$). Premature termination of the infusion in the D and DEx groups was rare.

Results of Stress Tests

In both the younger and elderly patients, the incidence of significant ST-segment depression in the DEx group was higher than in the D group ($P = .011$, $P = .022$). The AEx group showed a significantly higher incidence of significant ST segment depression compared with the A group ($P < .001$, $P = .037$) (Table 3). No significant differences were seen in the incidence of ischemic ST-segment depression between pharmacologic stress tests with exercise (DEx or AEx group) and the Ex group in both the young and elderly groups.

The proportions of patients who showed fixed or reversible perfusion defects were similar between the exercise and pharmacologic stress tests (D, DEx, A, and AEx) in both the young and elderly. No significant difference was found in the incidence of fixed or reversible perfusion defects between the D and DEx groups or between the A and AEx groups in both the younger and elderly populations.

DISCUSSION

Exercise Performance in the Elderly

We took 75 years old as a dividing point between the elderly and younger patients, because physiological differences quickly become apparent in this age range.[6,7] Our data showed that the elderly were able to exercise an average of 5 minutes compared with the younger average of 8 minutes with the Bruce protocol. The satisfactory completion rate of exercise stress testing was 54% in elderly as opposed to 67% in younger patients. Elderly patients are not ideal candidates for exercise stress testing, particularly with the Bruce protocol, even when the patient appears fit for exercise, unless physical capability was one of the questions.

Minimizing Adverse Effects By Exercise Supplementation

In this study chest discomfort, feelings of impending syncope, flushing, and a fall in blood pressure were more frequent in pharmacologic stress tests without exercise compared with the standard exercise stress test.[11-13] However, most of these symptoms were mild, transient, and well tolerated. It is interesting that exercise supplementation of the pharmacologic stress test

reduced the intensity and frequency of symptoms known to be associated with the systemic vasodilation caused by pharmacologic agents. Experimental data indicate that the vasodilator potency of adenosine is related to modulation of sympathetic neurotransmission.[14] Adenosine elicits presynaptic inhibition of norepinephrine release from the adrenergic nerve terminals.[15,16] Combining exercise with pharmacologic stress testing provides sympathetic stimulation, which increases heart rate and cardiac output. Therefore adverse effects associated with systemic vasodilator action, particularly symptoms associated with a fall in blood pressure, can be prevented.

Adenosine-Induced Atrioventricular Block

In this study adenosine stress test without exercise demonstrated an overall mean 12.9% incidence of atrioventricular block. This frequency was higher than that in the previous multicenter trial, which reported a 7.6% incidence of atrioventricular block.[13] However, the study population in the multicenter trial was younger (65 years old) than patients in the A group (the younger, 65 years old and elderly, 81 years old) in our study. Furthermore in our study the younger A group (median age 65 years) had a 7.9% incidence of atrioventricular block, comparable to the result of the multicenter trial. Therefore our data demonstrated that elderly patients are perhaps more susceptible to adenosine-induced atrioventricular block.

Adenosine-induced atrioventricular block[17,18] is known to be minimized by exercise supplementation.[19,20] However, this study demonstrated that exercise supplementation failed to reduce the incidence of adenosine-induced atrioventricular block in the elderly. Atrioventricular block seems unlikely to be caused by underlying CAD, because abnormal scan results were uncommon in patients who had adenosine-induced atrioventricular block in the elderly AEx group. Of 15 elderly patients in the AEx group who had atrioventricular block, only 3 patients showed abnormal scan results. Furthermore administration of digitalis or β-blockers is unlikely to be responsible, because the use of these medications was similar between elderly patients in the AEx group with (8 of 15, 53.3%) and without atrioventricular block (56 of 101, 55.4%). Elderly healthy subjects may have an intrinsic atrioventricular nodal dysfunction that is independent of β-adrenergic or parasympathetic influences.[21]

ST-Segment Depression

Pharmacologically induced ST-segment depression is a highly specific marker for CAD.[22,23] This has been explained by the "coronary steal phenomenon."[22-24] However, the multicenter trial demonstrated that the incidence of pharmacologically induced ST-segment depression was low.[11] In our study modest supplementary exercise during pharmacologic stress tests in the DEx and AEx groups produced an incidence of ST-segment depression similar to the standard exercise test. This finding may be related to an imbalance between myocardial oxygen supply and demand aggravated by the coronary steal phenomenon and exercise.[25] We believe that additional modest exercise supplementation to the pharmacologic stress test increases the probability of demonstrating ischemic ST segment changes.

Limitations

The ideal study design to compare the characteristics of the 5 different types of stress tests would be to perform all 5 stress tests in each patient. Unfortunately, such an approach is not feasible. Our analysis was based on groups of different patients. Significant differences in sex, incidence of risk factors, and use of medications were found between young and elderly groups. It has also been previously reported that there is a higher frequency of adverse effects among women during dipyridamole[26] and adenosine[11] infusion compared with men. Our results may be affected by physiologic and sex differences characteristic of younger and elderly groups.

This study demonstrated a relatively low frequency of some adverse effects such as flushing or headache compared with published data. All patients were asked, usually several times, how they felt and how they were doing. If the patient alluded to any symptoms, he or she was questioned in detail about all potential symptoms. Compared with the multicenter adenosine trial,[11] a higher incidence of wheezing suggesting bronchospasm was noted. This difference may be explained partly by inclusion of some patients with chronic obstructive pulmonary disease receiving bronchodilators.

CONCLUSION

1. The elderly (aged >75 years) group showed a high incidence of diabetes mellitus, hypertension, lower exercise capacity, and was less likely to achieve 85% of MPHR in exercise stress testing with the Bruce protocol compared with the younger patients.
2. Modest exercise supplementation of pharmacologic stress testing prevented the majority of adverse effects. Adenosine-induced atrioventricular block was not significantly affected by exercise supplementation in the elderly.
3. The frequency of ischemic ST changes in pharmacologic stress testing equaled that obtained in the exer-

cise stress testing when supplemented by modest exercise.

4. Although there were adverse events in these patients, there were no deaths, myocardial infarctions, or other major complications. This observation suggests that exercise and pharmacologic stress tests are equally safe in the elderly compared with a younger population.

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MAY 25 2000

U.S. PUBLIC HEALTH SERVICE

Steven Mark Rodin, M.D.
Medical Officer

Food Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

Medical Review of Geriatric labelling supplement

review last revised: 5/25/2000

NDA #:	20-059
Sponsor:	Fijusawa Healthcare
Drug:	Adenosine (Adenoscan®)
Submissions:	7/28/99, 8/6/99

Background

Eleven publications were reportedly captured by the sponsor's literature search, using methodology that was not fully described[1]. Patients and adenosine exposures were generally of the sort for which the drug is indicated for diagnostic use. The sponsor also submitted a listing of postmarketing adverse events (AE) reportedly observed through 6/23/99.

Safety data

Descriptions, even methodologically limited ones, of AE analyzed according to age were provided in only two of the submitted publications (i.e., Cerqueria et. al.[2] and Johnston et. al.[3])

We have previously reviewed the Cerqueria publication of registry data, and at that time noted that its limitations included its non-capture of the NDA's cases of fatal cardiac arrest and sustained AV block.[4] It is also noteable that Cerqueria's design was not randomized nor was the reported analysis(of AE by age)blinded.

In this prospective registry the frequency of early AE (occurring during and immediately after

[1] although a request was made for this description.
[2] Cerqueria MD. Verani MS, Schwaiger M, Heo J. Iskandrian AS. Safety profile of adenosine stress perfusion imaging: Results from the Adenoscan multicenter trial registry. J Am Coll Cardiol 1994;23:384-389.
[3] Johnston DL. Hodge DO. Hopfenspirger MR, Gibbons RJ. Clinical determinants of hemodynamic and symptomatic responses in 2,000 patients during adenosine scintigraphy. Mayo Clin Proc 1998:73:314-320.
[4] see my 6/15/95 Consultation Report to DDMAC regarding adenosine NDA 20-059.

adenosine infusion) was reported in 9256 patients of mean age 65 years. Atrioventricular (AV) block was reported at a higher mean rate in those ≥70 years (9.44%), relative to those <70 years old (7.05%), while in a different analysis the relative risk of *any* AE was lower in older patients (in this analysis "young" was defined, depending on gender, as either ≤65 or ≤68 years).

In the report of Johnston et. al., the posthoc nature of the analysis, and the multiplicity of comparisons renders the findings non-conclusive. Nearly equal numbers of subjects were non-elderly (<70 years) vs elderly (≥ 70 years), i.e. 1,003 vs 997, respectively. Some adenosine-associated effects were asserted to be nominally lesser in the elderly: i.e. lesser systolic BP lowering (3 mm Hg mean difference), less extensive tachycardia (4 bpm mean difference), and less severe chest pain.

The rest of the submitted publications provided no analyses of AE by age. These included the report of Abreu et. al.[5] on 607 patients of mean age 63 years, the publication of Cave et. al.[6] describing a 535 patient experience, the publication of Coyne et. al.[7] in patients of mean age 60 years, the report of Gupta et. al.[8] in patients of mean age 58 years, the publication of Iskandrian et. al.[9] in 148 patients of mean age 63 years, the work of Nguyen et. al.[10] in 60 patients of mean age 62 years, the report of Nishimura et. al.[11] in 101 patients of mean age 64 years, the report of Nishimura et. al.[12] in 101 patients of mean age 64 years, the publication of Verani et. al.[13] in 89 patients of mean age 64 years, and the abstract of Beer et. al.[14] describing 79 adenosine-exposed

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[5] Abreu A, Mahmarian JJ, Nishimura S, Boyce TM, Verani MS. Tolerance and safety of pharmacologic coronary vasodilation with adenosine in association with thallium-201 scintigraphy in patients with suspected artery disease. J Am Coll Cardiol 1991;18(5):730-735.

[6] Cave V, Wasserleben V, Heo J, Iskandrian AS. Age- and sex-related differences in the use of coronary angiography in patients undergoing adenosine SPECT thallium imaging. Cor Artery Dis 1993;4:1123-1127.

[7] Coyne EP, *et al.* Thallium-201 scintigraphy after intravenous infusion of adenosine compared with exercise thallium testing in the diagnosis of coronary artery disease. J Am Coll Cardiol 1991;17:1289-1294.

[8] Gupta NC, Esterbrooks DJ, Hilleman, DE, Mohiuddin SM. Comparison ofadenosine and exercise thallium-201 single-photon emission computed tomography (SPECT) myocardial perfusion imaging. J Am Coll Cardiol 1992;19:248-257.

[9] Iskandrian AS. Heo J, Nguyen T, Beer SG, Cave V, Ogilby JD, Untereker W, Segal BL, Assessment of coronary artery disease using single-photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia. Am J Cardiol 1991;67:1190-1194.

[10] Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single-photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia: Correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. J Am Coil Cardiol 1990;16:1375-1383.

[11] Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol 1991;18:73G-745.

[12] Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol 1991;18:73G-745.

[13] Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. Circulation 1990:82:80-87.

[14] Beer S. Heo J, Nguyen T, Cave V, Cassel D, Iskandrian AS. Assessment of coronary artery disease in the elderiy:

patients aged ≥65 years.

The sponsor's submitted listings of postmarketing AE provide no denominator data, and thus there are no comparative event rate data. Additionally there is missing documentation of age in a number of cases. No conclusive interpretation of those safety data is available. For the purpose of completeness it is noted that in these subgroups of undescribed size the reported cases of heart arrest or ventricular tachycardia respectively numbered 9 in the older group (≥65 years) vs 3 in the younger group (<65 years),[15] the cases of complete AV block numbered 4 in the older group vs 3 in the younger group, and the cases of hypotension numbered 8 in the older group vs 3 in the younger group.

Diagnostic data

The submitted publications did not provide an unambiguous assessment of relative diagnostic utility in respective age subgroups. The resolution of several epistemologic issues would require a higher degree of data detail than is typical for these publications. Among such matters are the necessity for 2 X 2 diagnostic concordance tables or at least derived estimates of the 95% confidence interval for specificity. The variance of the specificity estimate was problematically high even with the larger sample size afforded by pooling of age subgroups in the NDA database. In that pooled analysis the lower bound of the 95% confidence limit for specificity was already 37%. Other epistemologic diagnostic issues not readily resolved by these publications' general level of data detail include the distribution of population factors which contribute to false positive results, the diagnostic thresholds applied in characterizing a test as indeterminate (and thereby excludable from the analysis), the status and quality of blinding, and the rate of inter-observer variability.

Comparison of adenosine vs exercise SPECT thallium imaging. J Nucl Med 1991;32 (Suppl):968.

[15] the evaluation of these is further complicated by case attributions (e.g. syncope, convulsions) that raise the question of whether malignant ventricular arrhythmia was an occult underlying cause.

Recommendation:

Although the submitted data do not provide conclusive inferences about geriatric use, the Federal Register notice of 62: 45325, 1997 provides a basis for undertaking a conservative revision of labelling in such contexts. An adequate description would be provided by such language as:

DRAFT LABELING

/S/ M.D. 5/25/00

Steven Mark Rodin, M.D. Date
Medical Officer

cc: HFD-110/ division file, CSO, A.Karkowsky, *no copy to S.Rodin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Chemistry Review(s)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-059
3. Name and Address of Applicant (City & State) Fujisawa Healthcare, Inc. Parkway North Center 3 Parkway North Deerfield, IL 60015-2548		4. Supplement(s) Number(s) Date(s) ~~SGS-007~~ 7/28/99 SE8-007
5. Drug Name Adenoscan	6. Nonproprietary Name Adenosine	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Labeling		
9. Pharmacological Category An adjunct to thallium-201 myocardial perfusion scinigraphy in patients unable to exercise adequately	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 3 mg/mL	
14. Chemical Name and Structure 6-amino-9-beta-D-ribofuranosyl-9-H-purine		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

Geriatric Labeling Supplement

Geriatric Use subsection to the Precautions section was added. Also changes were made in the Carcinogenesis, Mutagenesis subsection to be consistent with that of Adenocard (NDA 19-937) as requested by FDA in its correspondence dated December 8, 1998 (response to NDA 19-937/S-015).

Insert - 4558G/Revised: August 1999 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. **Conclusions and Recommendations:**

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. **REVIEWER**

Name	Signature	Date Completed
Danute G. Cunningham	/S/	August 4, 1999

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

20059S07.SUP

/S/
8-4-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Administrative Documents

EXCLUSIVITY SUMMARY FOR NDA #20-059 SUPPL #__007____

Trade Name: Adenoscan Generic Name: adenosine

Applicant Name: Fujisawa Healthcare, Inc. HFD # 110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) ____SE8____

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:

____Geriatric subsection establishment_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

NO

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

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

YES /_X__/ NO /___/

If yes, NDA # 20-059_____ Drug Name _Adenoscan (adenosine) Injection

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

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

YES /___/ NO /___/

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

PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

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

Investigation #2

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

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Quynh Nguyen, Pharm.D___ Date August 30, 2001_____
Title: Project Manager

/S/

Signature of _____ Date _____
Division Director
Cardio-Renal Drug Products
HFD-110

cc: Original NDA Division File HFD-93 Mary Ann Holovac

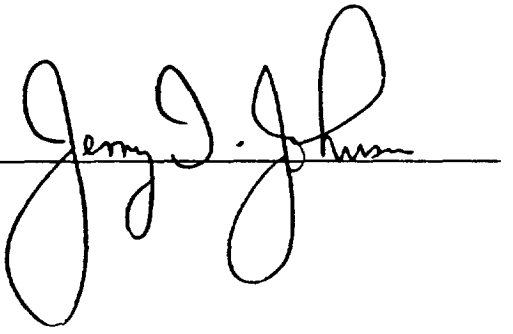
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Raymond Lipicky
8/31/01 12:13:44 PM

Debarment Certification

Fujisawa Healthcare, Inc., certifies that in support of this supplemental drug application, the company did not and will not use in any capacity the services of any person or firm debarred under sections 306 (a) or (b).

By: 

Date: 9 July 1999

Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

8-30-01

RHPM Approval Overview

Application: NDA 20-059/SE8-007
Adenoscan (adenosine) Injection, 3 mg/ml

Applicant: Fujisawa Healthcare, Inc.

Background: Fujisawa Healthcare, Inc. submitted NDA 20-059/SE8-007 that proposes, under the heading of **PRECAUTIONS**, the establishment of a **Geriatric Use** subsection. This supplement was submitted in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and older) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. The sponsor submitted 12 published articles to support the establishment of this subsection. In addition, SE8-007 provides for changes in the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, as requested in a December 8, 1998 letter from the Division to make this subsection consistent with a prior Adenosine application, NDA 19-937.

Fujisawa submitted this application on July 28, 1999, received July 29, 1999, but did not completely fill out the user fee cover sheet or pay the appropriate user fee. An Unacceptable For Filing (UN) letter was sent on August 5, 1999 informing the sponsor of the deficiencies. The company remitted payment and submitted an acceptable user fee sheet on August 11, 1999. The application was accepted for filing on August 11, 1999.

An approvable letter issued July 31, 2000 requesting final printed labeling with changes to Fujisawa's proposed **PRECAUTIONS/Geriatric Use** subsection. Fujisawa submitted final printed labeling in a submission dated January 16, 2001.

Medical Review:

Dr. Rodin's May 25, 2000 review states that "Although the submitted data do not provide conclusive inferences about geriatric use, the Federal Register notice of 62:45325, 1997 provides a basis for undertaking a conservative revision of labeling in such contexts. An adequate description would be provided by such language as:

PROPOSED LAbeling

In a June 5, 2000 addendum to his May 25, 2000 review, Dr. Rodin revised his recommendation to state: "Although the nature of the submitted data limits the conclusiveness of inferences about geriatric use, given the agreement of the Cerqueria evidence (discussed in my review of 5/25/2000) and these present Hashimoto data, I would strengthen the language of my prior labeling recommendation to include mention that elderly patients may be more vulnerable to adenosine-induced AV block."

(See Dr. Rodin's May 25, 2000 review and June 5, 2000 addendum.)

Group Leader's Review:

In his June 12, 2000 Group Leader's Memorandum, Dr. Karkowsky stated that:

"None of these publications either alone or in combination are adequate to determine that Adenoscan is a useful adjunct to the management or the decision making process in the elderly.

The relative safety of the cohort of patients defined as elderly in each of the study was qualitatively the same as those less senior. Quantitatively, the incidence of AV block was increased in the elderly versus less senior (17.8% versus 7.9% among those with Adenoscan and 13.0% versus 3.2% among those with Adenoscan plus exercise). The degree, intensity and reversibility of this A-V block were not stated. In this study the elderly were more likely discontinued prematurely from the infusion (14.9% versus 7.9% for those with Adenoscan and 5.3% versus 3.8% for those with exercise and Adenoscan)[1]. In a second study[2], age (>70) was an independent predictor of A-V blockade.

Consequently, some modification of the standard geriatric labeling appears reasonable.

> *Clinical studies of Adenoscan did not include sufficient number of subjects aged 65 years old and over to determine whether they respond differently from younger subjects. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out."*

(See Dr. Karkowsky's June 12, 2000 Memo.)

Chemistry Review:

Ms. Cunningham's review dated August 4, 1999 states that the supplement submitted on July 28, 1999 is satisfactory for the **DESCRIPTION** and **HOW SUPPLIED** sections.

Biopharmaceutics Review:

In an August 16, 2001 discussion, Dr. Marroum said that no biopharmaceutics review would be needed since the 12 published articles were not pharmacokinetic studies.

Comments/Recommendation

There are no issues pending with this efficacy supplement. The final printed labeling submitted on January 16, 2001 was revised in accordance with the approvable letter dated July 31, 2000, except for the following change:

Under **PRECAUTIONS**, in the first sentence of the **Geriatric Use** subsection, the word "number" as requested in the July 31, 2001 approvable letter was changed to "numbers" so that the sentence now reads: "Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently." This change is acceptable to Dr. Stockbridge.

In addition, the following changes were noted since the last approved package insert (approved December 10, 1997):

- The word "injection" has been added to follow the word "adenosine" throughout the package insert.

  This change is acceptable to Drs. Stockbridge, Zimmerman and Srinivasachar. The sponsor will be asked to make the corresponding change in the carton/container labeling to be consistent with the package insert at the time of their next printing and to report the change in their next annual report. This will be noted in the approval letter.

- Under **HOW SUPPLIED**, the statement: "**CAUTION**: Federal law prohibits dispensing without prescription." has been replaced with "**Rx only**."

  This change is provided for under the FDA Modernization Act of 1997.

An approval letter will be drafted based on final printed labeling for Dr. Lipicky's signature.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

qn/8-10-01/8-17-01/8-27-01

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

/s/

Quynh Nguyen
8/30/01 10:54:00 AM
CSO

RHPM Review of Final Printed Labeling

Application:	NDA 20-059/SE8-007 Adenoscan (adenosine) Injection, 3 mg/ml
Sponsor:	Fujisawa Healthcare, Inc.
Submission date:	January 16, 2001
Receipt date:	January 17, 2000
Type of Supplement:	Geriatric Labeling Supplement

Background:

Fujisawa Healthcare, Inc. submitted NDA 20-059/SE8-007 that proposes, under the heading of **PRECAUTIONS**, the establishment of a **Geriatric Use** subsection. This supplement was submitted in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and older) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. The sponsor submitted 12 published articles to support the establishment of this subsection. In addition, SE8-007 provides for changes in the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, as requested in a December 8, 1998 letter from the Division to make this subsection consistent with a prior Adenosine application, NDA 19-937.

An approvable letter issued July 31, 2000 requesting final printed labeling with changes to the proposed geriatric labeling subsection.

Review:

This submission provides for final printed labeling, revised in accordance with our approvable letter dated July 31, 2000 as follows:

1) The word "alkylxanthines" has been changed to "methylxanthines" in the first sentence of the second paragraph under **PRECAUTIONS/Drug Interactions.**

2) Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** the second paragraph has been changed from:

> Adenosine, however, like other nucleosides at millilmolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. In rats and mice, adenosine administered intraperitoneally once a day for five days at 50, 100, and 150 mg/kg [10-30 (rats) and 5-15 (mice) times human dosage on a mg/M^2 basis] caused decreased spermatogenesis and increased numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.
>
> to:

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.
Fertility studies in animals have not been conducted with adenosine.

3) Under **PRECAUTIONS**, the proposed **Geriatric Use** subsection has been changed from:

to:

Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

Note: The word "number" as requested in the July 31, 2001 approvable letter was changed to "numbers" in the first sentence: "Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently." This change is acceptable to Dr. Stockbridge.

In addition, the following changes were noted since the last approved package insert (approved December 10, 1997):

1) The word "injection" has been added to follow the word "adenosine" throughout the package insert.

This change is acceptable to Drs. Stockbridge, Zimmerman and Srinivasachar. Per Dr. Srinivasachar, the sponsor should be asked to make the corresponding change in the carton/container labeling to be consistent with the package insert at the time of their next printing and to report the change in their next annual report. This will be noted in the approval letter.

2) Under **HOW SUPPLIED**, the statement: "**CAUTION**: Federal law prohibits dispensing without prescription." has been replaced with "**Rx only**."

This change is provided for under the FDA Modernization Act of 1997.

Recommendation:

An approval letter should issue for this supplement.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

qn/8-10-01/8-17-01/8-27-01

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

/s/

Quynh Nguyen
8/30/01 10:59:24 AM
CSO

JUL 31 2000

CSO Review of Draft Labeling

Application: NDA 20-059/S-007

Applicant: Fujisawa Healthcare, Inc.

Document Date: July 28, 1999

Filing Date: August 11, 1999

Product Name: Adenoscan (adenosine) Injection, 3mg/ml

Background:

NDA 20-059/S-007 provides for geriatric labeling changes made in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. The sponsor submitted 12 published articles to support the establishment of this subsection in the labeling. In addition, the sponsor, at the request of a December 8, 1998 letter from the Division, proposed changes in the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection to make the labeling of this subsection consistent with a prior Adenosine application, NDA 19-937.

Fujisawa submitted this application on July 28, 1999, received July 29, 1999 but did not completely fill out the user fee cover sheet or pay the appropriate user fee. An Unacceptable For Filing (UN) letter was sent on August 5, 1999 informing the sponsor of the deficiencies. The company remitted payment and submitted an acceptable user fee sheet on August 11, 1999. The application was accepted for filing on August 11, 1999.

Review:

The sponsor submitted draft labeling revised as follows:

1. The word "alkylxanthines" has been changed to "methylxanthines" throughout the package insert.

2. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, the second paragraph has been changed from:

   Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. In rats and mice, adenosine administered intraperitoneally once a day for five days at 50, 100, and 150 mg/kg [10-30 (rats) and 5-15 (mice) times human dosage on a mg/M^2 basis] caused decreased spermatogenesis and increased numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.

   to:

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

3. Under **PRECAUTIONS**, a **Geriatric Use** subsection has been established. It reads as follows:

PROPOSED DRAFT LABELING

Dr. Karkowsky, in his June 12, 2000 medical review, revised the sponsor's above paragraph as follows:

> Clinical studies of Adenoscan did not include sufficient number of subjects aged 65 years old and over to determine whether they respond differently from younger subjects. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

Dr. Lipicky suggested minor modifications to Dr. Karkowsky's revision; his revision reads as follows:

> Clinical studies of Adenoscan did not include sufficient number of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

Comments/Recommendations:

I will draft an approvable letter for Dr. Lipicky's signature.

/S/

Edward Fromm
Consumer Safety Officer

dr/7-24-00

cc: NDA 20-059
HFD-110
HFD-110/EFromm/Blount

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-059/S-007

Correspondence

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	**(847) 317-7286**
Attention:	**Mr. Donald R. Peckels**
Company Name:	**Fujisawa Healthcare, Inc.**
Phone:	(847) 317-1587
Subject:	**Copy of Approval Letter and Approved Package Insert for NDA 20-059/S-007**
Date:	August 31, 2001
Pages including this sheet:	**8**

From: **Quynh Nguyen, Pharm.D.**
Phone: **(301) 594-5311**
Fax: **(301) 594-5494**

Dear Don,

Please find attached a copy of the approval letter and approved package insert for NDA 20-059/S-007 for Adenoscan (adenosine) Injection. If you have any questions, please feel free to contact me at the above numbers.

Thanks,
Quynh

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 2 0 1999

NDA 20-059/S-007

Fujisawa Healthcare, Inc.
Attention: Laurence R. Meyerson, Ph.D.
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Dear Dr. Meyerson:

Please refer to your labeling supplemental new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Adenoscan (adenosine) Injection, 3mg/mL.

You were notified in our letter dated August 5, 1999 that your supplemental application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your supplemental application has been accepted as of August 11, 1999.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 10, 1999 in accordance with
21 CFR 314.101(a).

The review priority classification for this application is standard.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:	Courier/Overnight Mail:
Center for Drug Evaluation and Research Division of Cardio-Renal Drug Products, HFD-110 Attention: Division Document Room, HFD-110 5600 Fishers Lane Rockville, Maryland 20857	Food and Drug Administration Center for Drug Evaluation and Research Division of Cardio-Renal Drug Products, HFD 110 Attention: Document Room, HFD-110 1451 Rockville Pike Rockville, Maryland 20852

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Project Manager
(301) 594-5311

Sincerely yours,

/S/ 8/20/99

Natalia A Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC:
Archival NDA 20-059/S-007
HFD-110/division file
HFD-110/D Willard
HFD-110 /Team Leaders and reviewers
DISTRICT OFFICE

Drafted by: dw/8/12/99
Final: asb/8/17/99
filename:20-059(ac).doc

ACKNOWLEDGMENT (AC)

CL for DW 8/18/99

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-059/S-007

AUG - 5 1999

Fujisawa Healthcare, Inc.
Attention: Laurence R. Meyerson, Ph.D.
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Dear Dr. Meyerson:

We acknowledge receipt of your supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Adenoscan (adenosine) Injection, 3mg/mL

NDA Number: 20-059

Supplement Number: S-007

Date of Supplement: July 28, 1999

Date of Receipt: July 29, 1999

This supplement proposes the following change(s):

1. Changing the word "alkylxanthines" to "methylxanthines" throughout the package insert.

2. Changing the second paragraph under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** from:

> Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. In rats and mice, adenosine administered intraperitoneally once a day for five days at 50, 100, and 150 mg/kg [10-30 (rats) and 5-15 (mice) times human dosage on a mg/M^2 basis] caused decreased spermatogenesis and increased numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.

to:

> Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

3. Adding a **Geriatric Use** subsection under **PRECAUTIONS** that states:

PROPOSED DRAFT LABELING

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this supplemental application is not accepted for filing. We will not begin a review of this supplemental application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: **This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number is on the enclosed check.**

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room HFD-110
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please contact:

Diana Willard
Regulatory Health Project Manager
(301) 594-5300.

Sincerely yours,

(S) 8/5/99

Natalia A Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research