DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 29 1999

Donald E. Baker, J.D.
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

RE: NDA 20-059
Adenoscan (adenosine)
MACMIS ID # 8429

Dear Mr. Baker:

This letter is in reference to Fujisawa Healthcare, Inc.'s (Fujisawa) promotional materials for Adenoscan. We specifically refer to an advertisement for Adenoscan published in the October 1999 issue of *The Journal of Nuclear Medicine*. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the advertisement and the World Wide Web Site (WWW) that it refers to, and has concluded that they are false and misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Omission of Pertinent Information--Failure to Disclose Full Indication

In the ad, Fujisawa claims that Adenoscan provides a "fast start," keeps vessels "wide open," and provides for a "rapid return" to baseline when used for pharmacologic stress. However, you did not disclose that the drug is indicated only for patients who are not able to exercise adequately. Pharmacologic stress agents are labeled for use in a limited population because they have serious side effects (some of these serious side effects are detailed in the "fair balance" section of this letter).

Lack of Fair Balance

The advertisement fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. Although information is presented regarding the potential for delayed side effects, you have not disclosed important warning information from the approved product labeling. Specifically you failed to include that:

1) Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

2) Adenoscan (adenosine) 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.

Requested Supporting Evidence

In the ad, you claim that Adenoscan has a lower cost-per-case than dipyridamole. Although you indicate that reference number 2 supports the claim, there are no references associated with the ad. We request that you submit data to support this claim.

World Wide Web Site (WWW)

Promotion of An Unapproved Use

In your WWW referred to in the ad, you state in the "pharmacological stress imaging" section[1] that pharmacologic stress agents are indicated for patients who can not exercise at maximal levels, usually due to physical inability or lack of motivation. You further state that pharmacologic stress agents may also be appropriate in patients with left bundle branch block, where they appear to deliver greater accuracy than exercise for myocardial perfusion imaging. This second statement promotes Adenoscan for an unapproved new use. Adenoscan is approved as an adjunct to Thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

1. The specific address of this page is:
HTTP://www.adenoscan.com/adenoscan/spectmonograph/pharmstressimage.htm (November 22, 1999).

Incorrect Statement

In the same section, you state that arbutamine is not approved for use in perfusion imaging. This statement is false because GenESA (arbutamine) System is approved for determining the presence or absence of coronary artery disease (CAD) in patients who can not exercise adequately.

Cost Comparison

On the same page, you present a table that compares the physical characteristics of Adenoscan and dipyridamole. Also in the table, you compare the total cost of each drug per patient and give a price range of each and a reference for the information. This cost comparison presentation is misleading because it is not clear to what the cost refers.

Monitoring Time

Also in the same table, you compare the percent of patients requiring extra monitoring time and show that Adenoscan is superior to dipyridamole. This comparison must be supported by substantial evidence.

Requested Supporting Evidence

We request that you submit the references by Hilleman DE, et al.[2] and Johnston DL et al.[3] for our review to support the above claims.

Failure to Submit Reports

DDMAC has no record that you submitted a copy of the advertisement to us via Form FDA 2253 at the time of initial publication of the advertisement. These submissions are required as part of the post-marketing requirements for a new drug application described in 21 CFR 314.81.

Fujisawa should immediately cease the dissemination of these violative materials and all similar promotional materials that contain the same or similar violative issues.

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2 . Hilleman DE, Lucas BD, Mohiuddin SM, et al. Cost-minimization analysis of intravenous adenosine and dipyridamole in thallous chloride Tl 201 SPECT myocardial perfusion imaging. *Ann Pharmacother.* 1997;31:974-979.

3. Johnston DL, Daley JR, Hodge DO, Hopfenspirger MR, Gibbons RJ. Hemodynamic responses and adverse effects associated with adenosine and dipyridamole pharmacologic stress testing: a comparison in 2,000 patients. *Mayo Clin Proc.* 1995;70:331-336.

Fujisawa should respond in writing to DDMAC regarding this issue by December 13, 1999. Your response should include Fujisawa's intent to comply with the above request and include the date that it ceased disseminating these and any other violative promotional materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Fujisawa that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 8429 and NDA 20-059.

Sincerely,

/S/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications