

**BRIEF SUMMARY**

**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. 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.

**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 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 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.

**Sinoatrial and Atrioventricular Nodal Block**

Adenoscan 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.

**Hypotension**

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

**Post Marketing Experience (see WARNINGS):** The following adverse events have been reported from marketing experience with Adenoscan. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors.

**Body as a Whole:** injection site reaction

**Central Nervous System:** Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

**Digestive:** Nausea and vomiting

**Respiratory:** Respiratory arrest

**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.

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

Rx only

Marketed by Astellas Pharma US, Inc.

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Manufactured by Hospira Inc.

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47101/Revised: September 2006

# Adjust Treatment Goals In Hypertensive Seniors

*In patients with coronary artery disease, pressure levels less than 120/80 mm Hg may be dangerous.*

BY MITCHEL L. ZOLER

Philadelphia Bureau

ORLANDO — Current blood pressure categories should not serve as treatment goals for older patients with hypertension and coronary artery disease, based on a post hoc analysis of data collected from more than 22,000 patients.

Among patients with hypertension and documented coronary artery disease (CAD) and an average age of 66, those who maintained a blood pressure of less than 120/80 mm Hg had a significantly higher rate of death, myocardial infarction, or stroke, compared with patients who were maintained at a pressure of 120-139/80-89 mm Hg, Rhonda M. Cooper-DeHoff, Pharm.D., reported in a poster at a conference on cardiovascular disease epidemiology and prevention sponsored by the American Heart Association. Further analysis showed that systolic pressure played the key role, and that patients did best if their systolic pressure was kept at 120-139 mm Hg.

These findings are noteworthy because the current standard for treating hypertension in the United States, the Seventh Report of the Joint National Committee (JNC 7), labeled blood pressures in the range of 120-139/80-89 mm Hg “prehypertension” and said that patients with these pressures need lifestyle modifications to lower their pressure and prevent development of cardiovascular disease.

A major difference between the prehypertensive people described in JNC 7 and the patients in the new analysis is that the new study focused on patients with existing CAD who were treated with antihypertensive medications to reach their maintenance blood pressure. The JNC 7 guidelines apply to previously untreated people, most of whom would not have CAD.

“Our findings suggest that blood pressure reduction in elderly hypertensive CAD patients is important, but care should be taken to avoid excessive blood pressure lowering in this population,” Dr.

Cooper-DeHoff and her associates said in their poster.

Blood pressure that is less than 120/80 mm Hg in older patients with CAD may be dangerous because these patients have relatively stiff arteries and it may be hard to adequately perfuse important organs at lower blood pressures, Dr. Cooper-DeHoff said in an interview.

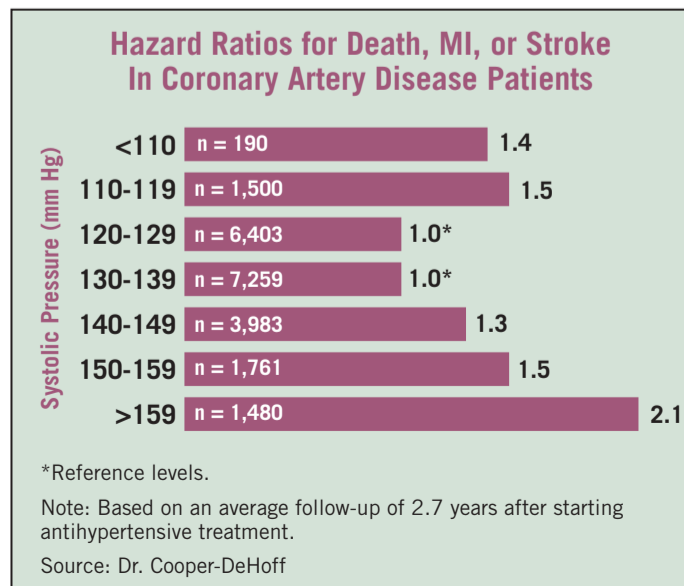
“The message isn’t to not treat hypertension in these patients, but to use caution and not treat to very low levels. The idea that the lower the pressure the better may not apply to these patients,” said Dr. Cooper-DeHoff, associate director of the cardiovascular clinical trial program at the University of Florida, Gainesville.

Her analysis used data collected in the International Verapamil-Trandolapril Study (INVEST), which was designed to compare two antihypertensive strategies in patients with CAD. The main finding from the study was that a blood pressure-lowering regimen based on using verapamil SR and trandolapril was as effective as a regimen based on using atenolol and hydrochlorothiazide (JAMA 2003; 290:2805-13). The post hoc analysis by Dr. Cooper-DeHoff and her associates focused on the outcomes of patients based on their achieved pressure with treatment rather than on their outcomes based on what treatment they received.

The analysis included data on 22,576 patients who were followed for an average of 2.7 years after starting their antihypertensive treatment. The patients were 50-90 years old, with an average age of 66. All participants had documented CAD. The primary outcomes tallied were death or nonfatal myocardial infarction or stroke.

One analytic approach divided the patients into three groups: about 1,500 patients who achieved an average pressure of less than 120/80 mm Hg, about 13,600 patients who reached a mean pressure of 120-139/80-89 mm Hg, and about 7,500 whose average pressure on treatment remained at or above 140/90 mm Hg.

In an analysis that adjusted for demographic and clinical differences at baseline, the patients with the lowest pressures had a 44% increased risk of a primary outcome, compared with patients in the middle group, and those with the highest pressures had a 53% increased risk of a primary outcome, compared with patients in the middle group. Both differences were statistically significant. ■



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