

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

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.

**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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## POLICY &amp; PRACTICE

## U.S. System Gets Failing Grade

The U.S. health care system ranked 15th out of 19 countries in number of preventable deaths, according to a comparison of 37 indicators of health outcomes, quality, access, equity, and efficiency. The United States scored particularly low, compared with other nations, on efficiency, getting an average score of 51 out of 100. The report blames this partly on the lack of electronic medical records—used by only 17% of American physicians, compared with the benchmark, which was 80% in the top-performing three nations in 2000-2001. Scores for quality and equity of access were highest, at 71. “Our purpose in issuing this scorecard is to bring attention to opportunities to improve, with benchmarks to motivate change,” said Dr. James Mongan, chairman of the 18-member commission that conducted the study and CEO of Partners HealthCare in Boston. “We applaud the commission for providing us with a comprehensive, comparative set of measures to use as a basis for improving the performance of our nation’s health care system,” the American Board of Internal Medicine said in a statement. The full report is available at [www.cmfw.org](http://www.cmfw.org).

## Target Opens In-House Clinics

Target, the Minneapolis-based retail powerhouse, is opening in-house clinics at 8 of its 1,443 stores. The company is rolling out the concept in its corporate hometown and soon will add at least four more in that region. According to Target, the clinics will feature a private waiting area and exam rooms and will offer services such as flu shots and treatments for strep throat, bronchitis, and skin conditions. Prices for services—most under \$50—will be clearly listed. The clinics are staffed by licensed nurse-practitioners and physician assistants. Medcor will provide clinic management, and physicians from Fairview Health Services will provide oversight and consultation. The company said in a statement that it will “meet or exceed the American Medical Association and the American Academy of Family Physicians guidelines for retail healthcare.”

## Low Physician E-Mail Use

Physicians are rarely using e-mail to communicate with patients, according to one study, and yet, patients overwhelmingly report that they would like to use e-mail to set appointments, talk with the doctor, and receive test results, according to a separate poll. The Center for Studying Health System Change found that only 24% of physicians said they used e-mail to discuss a clinical issue with a patient in 2004-2005, a 4% increase from the previous study period of 2000-2001. Almost half of physicians in academic settings and staff or group HMO practices use e-mail for clinical discussions, compared with about 20% in practices of 10 or fewer physicians. Physicians in nonmetropolitan areas or who have large numbers

of Medicaid and/or Medicare patients say they are less likely to use e-mail, because of patients’ lack of access to the technology. Some reasons for not using e-mail are lack of reimbursement for consultations, cost of implementing a secure system, and fears that e-mail will add to workloads. A recent Wall Street Journal–Harris Interactive poll of 2,624 adults found that 74% want to communicate directly with doctors by e-mail, 67% want to receive test results, and 75% want to schedule appointments via the Internet.

## Insurance Premiums Continue Rise

Employer-sponsored health insurance premiums rose 7.7% in 2006, outpacing wages and inflation, according to a report from the Kaiser Family Foundation and the Health Research and Educational Trust. The annual survey of employer health benefits found that on average, family health coverage costs \$11,480 annually, with workers contributing an average of \$2,973 toward their premiums. “We are still losing the race between premiums and workers’ earnings, and if that trend persists, employer-based coverage will continue to decline as fewer employers and workers can afford the cost of coverage,” Jon Gabel, coauthor of the study and vice president of the Center for Studying Health System Change, said in a statement. Most individuals opted for coverage through preferred provider organizations (60%), with others choosing HMOs (20%), point-of-service plans (13%), and conventional indemnity plans (3%). About 4% of individuals enrolled in high-deductible plans with a savings option. This year, about 7% of employers—mostly those with 1,000 workers or more—offered some form of high-deductible plan in 2006. The information is from a telephone poll of 3,159 randomly selected public and private employers. Details are available at [www.kff.org/insurance/7527](http://www.kff.org/insurance/7527).

## Reporting on Quality

More than 3,300 hospitals around the country have reported data on quality measures to Medicare and consumers, according to the Centers for Medicare and Medicaid Services. Of the 3,490 acute care hospitals eligible to participate in the federal program that links hospital payments to reporting of quality measures, 99% opted to report data. Under the program, hospitals that submit quality information to CMS are eligible to receive the full 2% payment update for inpatient services in 2007 under Medicare, while those who do not report will see a 2% payment reduction. “This is more evidence that paying for reporting and improving quality can help patients get better care,” Dr. Mark McClellan, outgoing CMS administrator, said in a statement. “Consumers can use this information to evaluate care, and doctors and hospitals can use it to help improve their performance.

—From staff reports