

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_e) and reduce arterial PCO₂, 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.

Adenoscan 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.

Deerfield, IL 60015

Manufactured by Hospira Inc.

Lake Forest, IL 60045 USA

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POLICY & PRACTICE

WHI Results Still Confusing

Just 18% of physicians said they have “no confusion at all” about the results of the Women’s Health Initiative study, according to an online survey of more than 400 physicians conducted on behalf of the Hormone Foundation. Also, only 15% said they believe patients accurately understand the risks of hormone therapy. The results “underscore the importance of physicians’ role in educating patients and [the public] on menopause management,” said foundation director Paula Correa. The survey, sponsored by Novogyne Pharmaceuticals, also found that 74% of physicians still consider hormone therapy as a first-line treatment for menopause symptoms. Novogyne manufactures the hormone therapy patches Vivelle-Dot, Vivelle, and CombiPatch.

Aventis Settles Pricing Fraud Case

Drugmaker Sanofi-Aventis has agreed to pay more than \$190 million to settle allegations of fraudulent drug pricing and marketing against Aventis Pharmaceuticals, one of its predecessor companies. According to the U.S. Department of Justice, Aventis used the difference between the inflated prices that were used to set reimbursement rates and the actual prices charged to customers to market the antiemetic Anzemet. In doing so, it caused fraudulent claims to be submitted to Medicare and other federal health care programs. The case arose after Ven-A-Care of the Florida Keys Inc. filed a False Claims Act suit, which allows a private person to file a whistleblower suit on behalf of government. To continue working with federal programs, Sanofi-Aventis agreed to report accurate prices. Almost \$180 million of the settlement will go to the federal government, and the balance will go to states and the District of Columbia. The whistle-blowers will receive about \$32 million.

Insurance Premium Increase Slows

Employer-sponsored health insurance premiums rose on average 6.1% in 2007, reflecting a continuing slowdown in premium increases. The 2007 premium increase is the smallest hike since 1999, according to an employer survey by the Kaiser Family Foundation and the Health Research and Educational Trust. But experts say the slowdown is likely temporary and isn’t providing relief to individuals or employers. In fact, the 6.1% increase is higher than the average increase in wages (3.7%) and in the overall inflation rate (2.6%). In 2007, the average premium for family coverage in the United States is \$12,106, with workers paying about \$3,281 for their share of the policy. The market continues to be dominated by preferred provider organizations, which insure about 57% of covered workers; consumer-driven plans account for only about 5%. For details, visit www.kff.org/insurance/7672.

ACS Seeks to Improve Access

The American Cancer Society has launched a national campaign aimed at

making access to health care for all Americans part of the national discussion and the number one priority of the next president. While the group is not advocating a specific plan, it has developed criteria for evaluating health care proposals. Under the principles developed by the American Cancer Society (ACS), the group defines “meaningful” health insurance coverage as adequate, affordable, available, and administratively simple. The idea is not just to provide access to cancer prevention, early detection, and treatment to the 47 million uninsured, but also to the tens of millions who are underinsured, John R. Seffrin, Ph.D., ACS chief executive officer, said during a news conference announcing the campaign. About 1 in 5 insured families touched by cancer will use up all or almost all of their life savings fighting the disease, he said. “For too many insured Americans, a cancer diagnosis is not only a personal health crisis, it is a prescription for financial ruin,” Dr. Seffrin said. The nationwide education campaign includes print and television advertisements, a Web site with information on how to take action, and grassroots activities by cancer activists. For more information, visit www.cancer.org/access.

Bill Seeks MD Gift Disclosure

Legislation in the Senate would require quarterly disclosure of gifts, honoraria, travel, and other payments to physicians by pharmaceutical, medical device, and biotechnology manufacturers. S. 2029 was introduced by Sen. Chuck Grassley (R-Iowa) and Sen. Herb Kohl (D-Wisc.) and would apply to manufacturers with more than \$100 million in gross revenues. The U.S. Health and Human Services Department would be required to make the disclosure data available on the Internet. Penalties would range from \$10,000 to \$100,000 per violation. Ken Johnson, senior vice president of the Pharmaceutical Research and Manufacturers of America, said in a statement that his group had not yet reviewed the bill but that contact with physicians is essential for education purposes. The group’s guidelines suggest gifts to physicians should not exceed \$100. The American Medical Association had also not yet read the proposal, but in testimony earlier this year, noted that it has extensive guidelines on accepting anything from industry.

Mass. Considers Retail Clinic Rules

Massachusetts’ Public Health Council is considering rules that would limit the scope of retail medical clinics in the state. The proposal is in response to a request by CVS Corp. to open 20-30 of its MinuteClinics in the Boston area beginning this fall. Under the proposal, applicants would need to state what services they intend to provide, develop policies that limit the number of times each patient could receive care there, and refer patients without a primary care physician to one in the area who is accepting new patients.

—Renée Matthews