

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.

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.

Deerfield, IL 60015

Manufactured by Hospira Inc.

Lake Forest, IL 60045 USA

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POLICY & PRACTICE

Uninsured Figures Climb

The number of people in the United States without health insurance edged higher in 2005, fueled in part by a drop in employer-sponsored health insurance, according to figures released in August from the U.S. Census Bureau. In 2005, 46.6 million people were uninsured, up from 45.3 million the year before. The percentage of people covered by employer-sponsored health insurance dropped from 59.8% to 59.5% between 2004 and 2005, while the percentage covered by government insurance stayed the same, according to the Census figures. The new figures, compiled as part of the Current Population Survey, showed that the number of uninsured children also increased. Between 2004 and 2005, the number of uninsured children rose from 7.9 million to 8.3 million. And children living in poverty were the most likely to be uninsured, with the uninsured rate at 19% for children living in poverty, compared with 11.2% of children overall in 2005. The American Medical Association issued a statement calling for action to address the uninsured problem. "The AMA plan for reducing the number of the uninsured advocates expanded coverage and choice through a system of refundable tax credits based on income, individually selected and owned health insurance, and market reforms that will enhance new, affordable insurance options," Dr. Ardis Hoven, an AMA board member, said in a statement.

Part D Premiums Hold Steady

Premiums under Medicare's Part D drug benefit will remain stable in 2007, according to figures released last month by the Centers for Medicare and Medicaid Services. Officials at CMS estimate that the average monthly premium paid by Medicare Part D beneficiaries will be about \$24 in 2007, nearly the same as in 2006. "Competition and choice in health care are working," Dr. Mark McClellan, CMS administrator, said at a press briefing. In addition to holding consumer costs steady, CMS officials reported that the national benchmark that determines Medicare's subsidy of drug coverage will decline next year. Competitive bids for the stand-alone drug plans and the Medicare Advantage managed-care prescription drug plans came in with lower-than-expected bids, according to CMS. The open enrollment period for 2007 starts Nov. 15.

Mixed Reviews for Merck

The most recent Vioxx court cases have produced mixed results for the drug-maker Merck & Co., Inc. In August, a Los Angeles jury ruled in the company's favor, finding that the Vioxx (rofecoxib) was not responsible for the heart attack of Stewart Grossberg, who had been taking the drug intermittently. Merck argued successfully that Vioxx was not responsible for Mr. Grossberg's heart attack because he has high cholesterol levels, atherosclerosis, and a family history of cardiac problems. But about two weeks later, a federal jury in New Or-

leans found Merck liable for \$51 million in damages in the 2002 heart attack of Gerald Barnett, a 62-year-old retired special agent with the FBI. The company is exploring grounds for appeal, including insufficient evidence and the application of incorrect legal standards, according to Merck. The company was also dealt another blow in August, when a New Jersey judge decided to set aside a 2005 jury verdict that had been in the Merck's favor. The judge ordered a new trial to take place early next year. The judge cited a December 2005 New England Journal of Medicine editorial expressing concerns about Vioxx-related study data as the basis for throwing out the jury verdict (N. Eng. J. Med. 2005;353:2813-4).

In the Dark on EC

Despite the controversy surrounding the provision of Plan B emergency contraception without a prescription (see story on p. 1), only about one-quarter of Americans in a recent survey said they had heard a lot about the debate. And nearly an equal number said they had heard nothing about the politically charged issue. The survey was commissioned by the Pew Research Center for the People & the Press and the Pew Forum on Religion & Public Life. The survey also found that about 48% of those surveyed favored selling emergency contraception without a prescription, whereas about 41% opposed the idea. The national telephone survey was conducted in July among more than 2,000 U.S. adults.

Drug Code Directory Incomplete

The Department of Health and Human Services' Office of Inspector General has found that the Food and Drug Administration's National Drug Code Directory is incomplete and inaccurate, largely as a result of drug companies' failure to submit required data, though the FDA shares some blame. The directory is supposed to be a current compendium of marketed drug products. The FDA relies on internal reports and on submissions from pharmaceutical manufacturers, which must report when a new product is introduced or withdrawn. The OIG report is a snapshot of the directory as of February 2005, when 123,856 products had unique entries. The OIG found that the listing left off just more than 9,000 drug products. For about 16%, the drug maker either had not submitted required forms or the agency had not appropriately processed them. Listings for about 5,100 products had been held up because the companies did not provide needed information. Finally, the OIG found that 34,000 products listed were no longer marketed or their entries contained erroneous information, mostly because drug makers had not told the FDA that the products were discontinued. In a comment, the FDA acknowledged many of the failures, but also said there was a decrease in the percentage of missing products since 1990.

—From staff reports