

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%	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.

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47101/Revised: September 2006

Undersized Stents Boost Thrombosis Risk 10-fold

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MUNICH — The most powerful risk factor for coronary stent thrombosis was undersizing of the stent, in a review of 437 episodes of stent thrombosis.

Other major risk factors for coronary stent thrombosis included stopping treatment with clopidogrel (Plavix), malignancy, less-than-ideal coronary blood flow following stent placement, and the presence of other significant coronary stenoses near the stented segment, Dr. Jochem W. van Werkum and his associates reported in a poster at the annual congress of the European Society of Cardiology.

The analysis also revealed that the patients with the greatest risk for stent thrombosis are those who receive one or more coronary stents to treat an ST-elevation myocardial infarction. The incidence of stent thrombosis in this group of 5,842 patients was 4.3%. Patients who received a stent for unstable angina or a non-ST-elevation myocardial infarction, 3,960 patients in the review, had a 1.8% rate of stent thrombosis; those stented to treated stable angina, 11,207 patients reviewed, had a 1.0% rate, reported Dr. van Werkum, a cardiologist at St. Antonius Hospital in Nieuwegein, the Netherlands, and his associates.

The Dutch Stent Thrombosis Study reviewed 21,009 patients who received at least one coronary stent at any one of several participating Dutch centers during January 2004–February 2007. The group included 437 patients with definite stent thrombosis. About 60% had received a bare-metal stent, and the remainder received a drug-eluting stent.

In 32%, the thrombosis appeared acutely after stenting (within 24 hours); in 41%, it occurred subacutely (within 30 days); in 13%, it occurred late (within 6 months); and in 5%, the thrombosis appeared very late (at least 6 months after placement).

To assess the role of various risk factors, the researchers did a case-control analysis that compared the prevalence of each factor among each patient who developed thrombosis (the cases), with two patients from the study who did not develop thrombosis (the controls). The cases and controls were matched for the clinical indication that led to stent placement, the date of their index procedure, and the center where the stenting was done.

For the entire group, stent undersizing (when the stent diameter is smaller than the coronary artery it's placed in) was linked with a greater than 10-fold increased risk of thrombosis. Less-than-ideal blood flow through the artery following stenting (less than TIMI grade 3 flow) was linked with an almost fivefold increased risk. Malignancy was linked with about a fourfold increased risk, as was a significant coronary stenosis just proximal to the stented region.

Other significant risk factors for thrombosis for all patients included dissection, no aspirin treatment, stenting at a bifurcation, a left ventricular ejection fraction of less than 30%, a significant stenosis distal to the stented segment, and multivessel disease. For every 10-year increase in the patient's age, the risk for thrombosis fell by 17%.

An early halt to clopidogrel treatment was another potent risk factor, although its impact varied depending on when treatment stopped. When clopidogrel stopped during the first 30 days, the risk was boosted 36-fold. Stopping clopidogrel between 30 days and 6 months increased the risk more than fourfold, and stopping clopidogrel after 6 months boosted the risk for thrombosis by nearly sixfold.

The analysis also assessed risk factors in several subgroups of patients. Among those who received a stent for unstable angina, the top risk factors were undersizing, significant coronary disease distal to the stented segment, and malignancy. ■

Risk Factors for Stent Thrombosis

RISK FACTOR	ODDS RATIO FOR RISK CHANGE
Clopidogrel halted < 30 days after stent placement	36.5
Undersizing of stent	10.7
Clopidogrel halted > 6 months after stent placement	5.9
Poor coronary blood flow after stenting (TIMI grade < 3)	4.7
Clopidogrel halted 30 days to 6 months after stent placement	4.6
Malignancy	4.4
Coronary stenosis of at least 50% proximal to stented segment	4.2
Dissection	3.6
No aspirin	2.6
Stent placed at bifurcation	2.5
Left ventricular ejection fraction less than 30%	2.2
Coronary stenosis of 50% or greater distal to stented segment	1.9
Multivessel disease	1.7
Increased age (for each additional 10 years)	0.83

Note: Based on a study of 21,009 patients who received at least one coronary stent. All odds ratios are statistically significant.

Source: Dr. van Werkum