

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 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.
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On-Call Issue Dominates EMTALA Panel Meeting

BY JENNIFER SILVERMAN

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WASHINGTON — On-call emergency care dominated the agenda at the inaugural meeting of the Department of Health and Human Services technical advisory group on the Emergency Medical Treatment and Labor Act.

EMTALA, enacted in 1986 to ensure public access to emergency services regardless of ability to pay, requires hospitals to maintain a list of physicians who are on call to the emergency department. Hospitals have the discretion to maintain these lists in a manner that “best meets the

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needs” of the hospital's patients. The Medicare Modernization Act of 2003 required HHS to establish a technical advisory group to review EMTALA regulation. While the obligation to provide the on-call list falls on the hospital, physicians assume new liability and other obligations once they agree to take on-call responsibilities, Charlotte Yeh, M.D., an emergency physician and advisory group member, said in an interview.

Hospitals cannot force physicians to be on call, although individual hospital policies may require on-call services as a condition for having privileges, she said. “Factor in issues such as reimbursement, and the physician is asking himself: Why should I do this? And that's how physicians get into the EMTALA debate.”

Hospitals testified that their emergency care was suffering due to physicians' unwillingness to provide on-call services.

“It has become increasingly difficult for hospitals to manage their on-call rosters in a manner that best meets the needs of their patients because of their trouble filling on-call slots,” said Jeff Micklos, vice president and general counsel for the Federation of American Hospitals. “There no longer is any certainty that an on-call physician will report for duty when called,” he said.

Physicians say that economic, practice, and lifestyle considerations affect their desire and ability to provide on-call coverage. As a result, they'll either refuse to be on call, or want to be paid ever-increasing fees, “which adds to EMTALA's practical effect as an unfunded mandate for hospitals,” Mr. Micklos said.

Physician-owned specialty hospitals, already a volatile issue, have exacerbated the on-call issue, said Mary Beth Savary Taylor, who spoke on behalf of the American Hospital Association. “Physicians who own limited-service hospitals often refuse to participate in emergency on-call duty at community hospitals, leaving them struggling to maintain [emergency department] specialty coverage.”

Hospitals are at a disadvantage, as they can be terminated from Medicare and

Medicaid for any kind of noncompliance under EMTALA, whereas physicians are terminated only in cases where the violation is “gross, flagrant, and repeated,” Ms. Taylor said. To provide hospitals with some type of due process, the Centers for Medicare and Medicaid Services should revise its regulations to establish an administrator-level appeals process—before a CMS regional office issues a finding of noncompliance and public notice of termination, she said.

Leslie Norwalk, CMS deputy administrator, told advisory group members that the agency could issue guidelines to hospitals on how they could protect themselves from lawsuits. “We'd like to help so courts will not punish [hospitals] for doing the right thing,” she said.

Mr. Micklos asserted that the statute's obligations should apply equally to hospitals and physicians, noting that a hospital “can only can be as good as the physicians on its medical staff.”

EMTALA states that on-call coverage is a joint decision between hospital administrators and physicians who provide on-call coverage, said Jason W. Nascone, M.D., who testified on behalf of the American Association of Orthopaedic Surgeons and the Orthopaedic Trauma Association.

“But it is unrealistic to expect physicians to work together with hospitals in developing and implementing on-call plans if physicians aren't included as equal partners with more authority, oversight and control, in the development and implementation of these plans,” Dr. Nascone said.

Interpretive guidelines developed to clarify hospitals' EMTALA responsibilities should be amended to further encourage true partnership arrangements between hospitals and physicians, Dr. Nascone said.

Physician groups urged CMS to adopt an affirmative rule prohibiting hospitals from requiring physicians to provide 24-7 emergency call coverage.

“We support the rule that physicians are not required to be on call at all times, but we fear that this provision doesn't go far enough to protect on-call physicians from nevertheless being required by hospitals to provide continuous emergency on-call coverage,” Alex B. Valadka, M.D., who spoke on behalf of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, testified.

The group will be advising HHS on issues related to EMTALA. It includes hospital, physician, and patient representatives, in addition to CMS and state officials and one representative from a Quality Improvement Organization.

No recommendations were issued at the meeting, although a subcommittee was formed to address on-call concerns. ■