

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 Hespira Inc.
Lake Forest, IL 60045 USA

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Medicare Proposal Targets ASC, Outpatient Payments

BY ALICIA AULT

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In a sweeping, 1,000-page proposal, the Centers for Medicare and Medicaid Services is seeking to change how it pays for procedures performed in outpatient departments and at ambulatory surgery centers. Two goals are to rein in rising outpatient expenses and to level the payment differential between ASCs and outpatient departments.

In a statement, CMS Administrator Mark McClellan said that it was time to look more closely at outpatient payments: “Doing nothing is not sustainable from the standpoint of Medicare costs and beneficiary premiums, and we want public input on the best approaches to promoting high-quality, affordable care.”

With 12% growth in 2006 and projected growth of 10% for 2007, outpatient costs are putting a squeeze on beneficiaries, who must make 25% copayments, Dr. McClellan said during a press conference sponsored by the agency.

CMS is proposing that hospitals receive an average 3% increase in outpatient payments if they submit quality data on the inpatient side. Hospitals would be required to report on patient satisfaction to receive the full inpatient and outpatient update. They would also report risk-adjusted outcome measures, including 30-day mortality for acute myocardial infarction, heart failure, and pneumonia, and three measures from the Surgical Care Improvement Project. The agency said it anticipates asking for outpatient quality data as outpatient-specific measures are developed.

Hospitals that do not submit quality data will be penalized. Instead of the full outpatient rate, they’ll receive the outpatient update minus 2%. Overall, outpatient spending—which covers general acute care hospitals, inpatient rehabilitation facilities, inpatient psychiatric facilities, long-term acute care hospitals, children’s hospitals, and cancer hospitals—will hit \$32.5 billion in 2007 under the proposed rule.

The agency is also proposing to increase from three to five the number of payment levels for visits to an outpatient clinic or emergency department. The maximum payment for clinic visits would be \$133, up from \$92, and emergency department visits would rise from \$244 in 2006 to \$345 in 2007. CMS also would create a new set of Healthcare Common Procedure Coding System (HCPCS) codes for visits to dedicated emergency departments (DEDs) subject to the Emergency Medical Treatment and Labor Act. The new codes would help CMS determine the relative cost of services provided at DEDs compared with emergent care furnished at a 24-hour-a-day, 7-day-a-week facility.

Most individual outpatient procedures will receive a small increase in reimbursement, but some are also slated for a reduction. Insertion, replacement, or repair of an implantable cardioverter defibrillator lead would be covered at \$22,800 in 2007, up from \$22,300 in 2006, and inser-

tion or replacement of a pacemaker pulse generator would be paid at \$16,400, up from \$10,000, according to Washington Analysis, LLC, which follows Medicare developments for Wall Street.

Drug infusion devices would receive relatively large increases of 23%-56% but neurostimulator implantation would decrease from \$11,600 in 2006 to \$10,800, according to the report by Washington Analysis.

The rule would also change how hospitals are paid for drug infusions. Currently, hospitals are paid the same for each type of infusion, whether it takes an hour or several hours. Under the new rule, hospitals would be paid for the initial hour plus additional fees for more hours. They also would receive a larger payment for complex drug administration.

On the ASC side, the goal “is to help our beneficiaries get the outpatient care they need in the most appropriate setting, by eliminating payment differences that inappropriately favor one outpatient setting over another and that may add to Medicare costs,” said Dr. McClellan in the statement.

In 2007, CMS is proposing to cap the amount paid to ASCs at no more than the reimbursement for outpatient departments, to produce at least \$150 million in savings. The agency also proposed to add 14 more procedures to the list of what it will cover at ASCs in 2007—including wound repair, percutaneous vertebroplasty, repair of venous blockage, ligation of hemorrhoids, and percutaneous transcatheter stent placement—and another 763 procedures in 2008. Any procedure that is considered safe and does not require an overnight stay would be considered eligible for Medicare reimbursement in 2008.

ASCs said they had no objection to bringing payments in line with those received by outpatient departments. But the industry was upset over CMS’s proposal for a 2-year phase-in of a new payment system, beginning in 2008. By 2009, ASCs would be reimbursed at 62% of the outpatient rate. The industry—which includes about 4,500 centers—had been hoping to receive 75% of the outpatient rate.

“The proposed payment rate will result in Medicare beneficiaries and the Medicare program paying more for outpatient surgery because patients’ only choice for many surgical procedures will be the more costly hospital setting,” said Kathy Bryant, president of the Federation of Ambulatory Surgery Centers, in a statement. The proposed rate will discourage many ASCs from offering certain procedures, said Ms. Bryant.

In a statement, the American Association of Ambulatory Surgery Centers called on members to submit comments to CMS objecting to the new proposal and to do the same with their congressional representatives.

CMS is receiving comments on the outpatient and ASC-payment proposal until October 10. A final rule will be published later in the fall, said the agency. ■