

## 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<sub>e</sub>) and reduce arterial PCO<sub>2</sub> 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, 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

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# Pulmonary Hypertension Misdiagnosed in the Obese

BY BRUCE K. DIXON

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MONTREAL — Obese patients often have a constellation of physiological problems that together can lead to a mistaken diagnosis of pulmonary artery hypertension, according to researchers at Duke University Medical Center in Durham, N.C.

The presence of exertional dyspnea in these patients often leads to an echocardiogram and a finding of elevated right ventricular systolic pressure. "Often the pressure is just mildly elevated, and these patients don't really have pulmonary arterial hypertension but are referred for evaluation anyway," Dr. Terry A. Fortin said at the annual meeting of the American College of Chest Physicians.

To assess diagnostic strategies for pulmonary arterial hypertension (PAH) in this often very symptomatic population,



**Factors that can contribute to a mistaken diagnosis of PAH include systemic hypertension and obesity.**

DR. FORTIN

Dr. Fortin and her colleagues at Duke University retrospectively assessed consecutive cardiac catheterization data on patients referred for suspected PAH.

Suspected PAH was defined as mean pulmonary arterial pressure (mPAP) greater than 25 mm/Hg, pulmonary capillary wedge pressure (PCWP) less than 15 mm/Hg, and pulmonary vascular resistance (PVR) greater than 3 Wood units. Patients with left ventricular systolic dysfunction, PAH clearly associated with a known syndrome, or significant valve or lung disease of sufficient severity to explain PH were excluded. That left 78 obese patients with mild pulmonary hypertension (PH) with mPAP greater than 25 mm/Hg and PVR less than 5 Wood units, said Dr. Fortin of Duke University Medical Center.

Of those 78 patients, 40 had baseline syndromes or conditions that the investigators believed adequately explained the patients' PH after work-up. Those conditions included connective tissue disease, congenital heart disease, chronic thromboembolic disease, portopulmonary disease, severe lung disease, high-output arteriovenous shunts, and left-sided valve disease.

Eliminating these patients left 38 patients with elevated mPAP associated with a constellation of factors that together resulted in PH, although maybe not PAH, Dr. Fortin said. Most were women with a mean age of 60 years. All were hypertensive, and virtually all had a body mass index greater than 30; half had a body mass index (BMI) greater than 40. Nearly two-thirds had diabetes and/or a sleep disorder.

"The precatheterization diagnostic tests often showed elevated right ventricular

systolic pressures on referral cardiac echo, and that was typically the reason that the patients were sent to us," Dr. Fortin explained. Many of the patients did have increased artery sizes, and their right atrium size or decreased contractility in the right ventricle was of concern. About half the patients were hypoxemic, and some were hypercarbic, "which is not necessarily what we would expect in pulmonary hypertension," Dr. Fortin added.

Low lung volume was common, and many patients had reduced diffusion capacity of carbon monoxide (DLCO). Two patients had only increased right ventricular systolic pressures.

"Looking at the cardiac cath data, PVRs were not quite 3 [Wood units] in most patients, and if you break them down into those with enlarged and normal right ventricles, they're slightly different, but not statistically so," she said. The investigators also found a slight but statistically non-significant difference in mean pulmonary pressures, with a predominance of elevated pressures, as expected in bigger right ventricles. Overall, the patients had normal cardiac indices and were not very sick.

Only one patient had pulmonary arterial hypertension based upon a PCWP less than 15 mm/Hg and a PVR greater than 3, Dr. Fortin said. Hypoxemia, hypercarbia, low total lung capacity, and DLCO were all related to obesity, hypoventilation, and sleep disorders, she noted.

"Lest you think that obese people do not ever have pulmonary hypertension, I was quickly able to glean 13 patients ... who were morbidly obese with BMIs greater than 40 who were seen in our clinic," Dr. Fortin said. "All had mPAPs greater than 25 with elevated pulmonary vascular resistances. In fact, their average pulmonary artery pressure was 60, and their PVR was 12, while their cardiac indices were very low; these were very sick patients."

The study's researchers concluded that a number of factors can contribute to a mistaken diagnosis of PAH, including systemic hypertension, obesity, sleep-disordered breathing and hypoventilation, and elevated pulmonary capillary wedge pressure.

"It should not be assumed that patients with an elevated right ventricular systolic pressure by echo have pulmonary arterial hypertension," Dr. Fortin cautioned. "Pulmonary capillary wedge pressure and diastolic dysfunction may be causative."

Aggressive management of weight, sleep disorders, hypertension, hypoxemia, and diabetes may limit the development of diastolic dysfunction and secondary pulmonary hypertension, though that's easier said than done, she added.

"Patients with this complex of disorders often have findings similar to those in full-blown PAH, and thus cardiac catheterization is necessary to help sort this out," Dr. Fortin explained. "I think that diagnostic testing also should definitely include sleep studies, as 70% of these patients had sleep disorders that were not necessarily diagnosed at the time of presentation." ■