

## 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, 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.

Lake Forest, IL 60045 USA

47101/Revised: September 2006

# Experts Discuss Options For Rosiglitazone Use

BY MIRIAM E. TUCKER

Senior Writer

CHICAGO — Until the controversy surrounding rosiglitazone has been resolved, physicians might consider the advice offered by three diabetes specialists during a panel discussion held during the annual scientific sessions of the American Diabetes Association.

The 2-hour session drew an overflow crowd despite being a last-minute addition to the already jam-packed ADA program. It featured presentations from Dr. Steven E. Nissen and Dr. Philip D. Home, along with panelists Dr. David M. Nathan, Dr. Barry J. Goldstein, and Dr. John B. Buse.

Dr. Nissen, of the Cleveland Clinic, reviewed the results of his meta-analysis of 42 trials that revealed a significant increase in the risk of myocardial infarction with rosiglitazone (N. Engl. J. Med. 2007;356:2457-71).

Dr. Home, of Newcastle University, Newcastle upon Tyne, England, then summarized the inconclusive findings of the 3.75-year analysis of data from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study, designed as a 6-year trial to assess the safety of rosiglitazone. The unplanned interim analysis had been published rapidly in response to the media attention (N. Engl. J. Med. 2007 June 5 [Epub doi:10.1056/NEJMoa073394]) and Congressional scrutiny garnered by Dr. Nissen's report.

Dr. Nathan, who is chief of the Diabetes Center at Massachusetts General Hospital, Boston, and who wrote editorials for both Dr. Nissen's and Dr. Home's articles, remarked, "There are insufficient data to come to any conclusions that would convince us all. That has given rise to this enormous controversy."

A joint meeting of the Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, scheduled for July 30, is likely to bring forth more data.

In the meantime, Dr. Buse, Dr. Goldstein, and Dr. Nathan offered advice about how they would approach the following three clinical scenarios:

► **A patient with diabetes in poor control who is not currently taking rosiglitazone.** Dr. Buse and Dr. Nathan agreed that they would not start a patient on rosiglitazone (Avandia) at this point, at least until more data become available.

"I think at this time, I wouldn't personally choose to start someone on Avandia therapy de novo until these issues are settled to the extent that they're likely to be settled in the next few months," Dr. Buse said.

Dr. Nathan pointed out that the well-known adverse lipid profile of rosiglitazone, compared with pioglitazone, already made it a less attractive option. Indeed, he said, the data on fluid retention and heart failure—combined with the newer data on fractures and decreased bone density—render the whole thiazolidinedione (TZD) class

less attractive than other agents. "I don't understand why people would, given the choice of other agents to lower glycemia, start anyone on rosiglitazone," he said.

But Dr. Goldstein suggested that rosiglitazone in low doses might still play a role in combination therapy in patients with insulin resistance. He advised following the ADA's treatment algorithm, published in 2006, which recommends metformin as first-line therapy with the TZDs as a possible add-on in patients who don't achieve glycemic goals (Diabetes Care 2006;29:1963-72).

"There's no reason to start with a TZD as monotherapy unless the patient is intolerant to metformin. But at a lower dose, they can be used in combination," said Dr. Goldstein, director of endocrinology, diabetes, and metabolic disease at Jefferson Medical College, Philadelphia.

► **A patient with diabetes who is in good control on a regimen that includes rosiglitazone.** All three panelists felt that they wouldn't rock the boat in this situation. "If [hemoglobin] A<sub>1c</sub>, LDL cholesterol, triglycerides, and [HDL cholesterol] are all controlled, I think there would be more risk to switching someone ... over the next 1.5-2 months ... until we know everything we're going to know for the next 2 years," when the RECORD results are available, Dr. Buse said.

Dr. Goldstein said that such a patient "should certainly stay on either [TZD] until we learn more." And, said Dr. Nathan, "I would think twice about changing someone who's achieving all the other goals."

► **A patient with diabetes who is taking rosiglitazone but is not in good control.** All three felt that consideration should be given to stopping rosiglitazone in this situation. Dr. Buse remarked, "If you're going to have to rethink the regimen, I think it's appropriate to rethink the Avandia as well." But even then, he added, it might be difficult to take a patient off the drug because of either personal preference or formulary issues.

Dr. Goldstein noted that such patients are often taking several oral glucose-lowering agents, most commonly metformin and a sulfonylurea in combination with a TZD, and that insulin is generally considered to be the next step. Given that it's rare for patients to be on insulin combined with three oral agents, and that the weight gain and fluid retention problems associated with TZDs are often exacerbated by insulin, "the TZD is often the one that's dropped when insulin is added."

But Dr. Nathan was more direct: "If the patient is not achieving goals, I would stop Avandia and change the regimen."

Dr. Buse disclosed no financial ties with either GlaxoSmithKline Inc., maker of rosiglitazone, or Takeda Pharmaceutical Co., maker of pioglitazone. Dr. Goldstein has ties to both, whereas Dr. Nathan has received research support from GSK. All three have relationships with makers of other diabetes drugs. ■