

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%	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.

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Manufactured by Hospira Inc.

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Torcetrapib Failure May Not Doom Other Drugs in Class

BY MICHELE G. SULLIVAN

Mid-Atlantic Bureau

The demise of torcetrapib may be a “bitter disappointment” to researchers, but it’s too soon to give up on the entire class of HDL cholesterol-raising agents, several of which are still under development, experts say.

“While this is a huge setback for the field of lipid therapy, it would be a big mistake for patients and physicians to get the impression that this research is a lost cause,” said Dr. Frederick Samaha of the University of Pennsylvania, Philadelphia. “There are several different drugs being looked at. We can’t presume from the failure of one that all of them will have similar problems.”

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, was furthest along that pipeline, however, and was the only one in a phase III trial (ILLUMINATE). The study randomized 15,000 patients with existing coronary heart disease to atorvastatin alone or to a combination of atorvastatin and torcetrapib.

But Pfizer Inc. abruptly halted it after an interim data analysis showed significantly more deaths in the combination arm than in the monotherapy arm (82 vs. 51). Although details haven’t been released, the imbalance in mortality appears to have been driven by cardiovascular events, Dr. Samaha said in an interview.

“It’s very disappointing. Of all the HDL-raising drugs, this class holds the most promise. [CETP inhibitors] increase HDL by 50%-100%, much more than even the second most effective drug, niacin. So we had a lot of really high hopes for torcetrapib.”

The question facing researchers, he said, is whether the mortality risk associated with torcetrapib will extend to any of the other CETP inhibitors under development by Hoffmann-La Roche Inc., Merck & Co., AstraZeneca Pharmaceuticals LP, and Bayer Pharmaceuticals Corp. “We can’t tell right now whether this is a class effect, or whether it’s specific to this one drug alone,” said Dr. Samaha, who is investigating the effect of niacin plus statins on cardiovascular events in the AIM-HIGH trial.

There are two possible culprits behind the increased mortality among torcetrapib patients, he said: the drug’s hypertensive effects, which caused significant blood pressure hikes in a small number of patients in the phase II studies, and accelerated atherogenesis.

Blood pressure effects are likely to be drug specific, as other CETP inhibitors in development haven’t thus far shown similar problems. But a finding that torcetrapib, a drug designed to prevent or decrease atherosclerotic plaque, actually increases it could have devastating implications for all CETP research. “That would most likely be a class effect that we would see with any of these drugs,” said James McKenney, Pharm.D., a primary investigator for torcetrapib’s 2006 safety and efficacy studies.

CETP inhibitors increase HDL cholesterol by limiting the amount of cholesterol that leaves the HDL particle, Dr. Samaha said. “What you end up with is larger HDL particles with more cholesterol associated with them. Whether those particles are still as cardioprotective [as normally occurring HDL] is something we don’t know.”

He’s not alone in voicing this concern. Boosting HDL levels this way has always been a controversial idea, according to Dr. Michael Davidson, director of preventive cardiology at Rush University Medical Center, Chicago. But despite uncertainty about the cardioprotective effects of CETP-modulated HDL cholesterol, he said in an interview, “a lot of us were still optimistic, because the 50% increase in HDL that we saw in the earlier studies was so significant that it should have resulted in a significant mortality risk reduction.”

That reduction should also have been large enough to offset the potential problem of hypertension, said Dr. Davidson, who worked with Dr. McKenney on the phase II studies (J. Am. Coll. Cardiol. 2006;48:1774-81; 1782-90).

In those studies, blood pressure increases were widely variable in both groups; however, significant jumps—systolic increases greater than 10 mm Hg from baseline or diastolic increases greater than 15 mm Hg from baseline—occurred in only about 3% of patients. “It was a concern,” Dr. Davidson said, “but we thought raising the HDL that much would offset any potential risks. Obviously, this blood pressure issue may be much more serious than we first imagined.”

While Pfizer has yet to release the causes of the deaths in its phase III study, Dr. Davidson thinks the drug’s hypertensive effects may play into the picture. “Perhaps we didn’t see a clear signal about this in the earlier trials because they included relatively healthy subjects, while the phase III trial involved sicker patients who had pre-existing cardiovascular disease.”

But because the other CETP inhibitors under development haven’t shown any effect on blood pressure thus far, torcetrapib may be an outlier among them. “It may just be a specific issue to this drug. I believe this class of drugs still has a lot of potential.” However, he cautioned, until the deaths in both arms of the ILLUMINATE trial have been adjudicated, it will be impossible to understand the drug’s full risk picture.

Two upcoming imaging trials will provide valuable additional clues to torcetrapib’s risks. One of these, the ILLUSTRATE trial, uses intravascular ultrasound to evaluate atherosclerotic plaque burden, said Dr. Steven Nissen, a principal investigator in that study.

ILLUSTRATE included 1,190 patients randomized to the combination of torcetrapib and atorvastatin or to atorvastatin alone. Data collection is complete; Dr. Nissen, medical director of the Cleveland Clinic Cardiovascular Coordinating Center, said he will present the results at the American College of Cardiology meeting in March. ■