

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%	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.

DOSE 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

Biodegradable DES Shown As Effective, Safe as Cypher

BY MIRIAM E. TUCKER

Senior Writer

WASHINGTON — A biodegradable, polymer-based, rapamycin-eluting stent developed by a group in Germany is at least as effective as the Cypher stent, Dr. Julinda Mehilli reported at a conference on transcatheter cardiovascular therapeutics, sponsored by the Cardiovascular Research Foundation.

Although the use of polymers in drug-eluting stents (DES) may provide better release kinetics of the drug, their permanent presence in the vessel is believed to have a negative impact on the long-term outcome. Polymer-free and biodegradable polymer-based DES are two potential approaches to eliminate the presence of permanent polymers, said Dr. Mehilli, of the Technical University, Munich.

In this study, called ISAR-TEST 3, the investigators compared both the polymer-free (PF) rapamycin-eluting stent and a rapamycin-eluting stent that uses a mixture of biodegradable polymer (BP) and natural resin with the permanent polymer rapamycin-eluting stent Cypher in a randomized trial involving 605 patients with coronary artery disease: 202 were randomized to BP DES, 202 to Cypher, and 201 to PF DES. About a third of all three groups had unstable angina and a history of myocardial infarction, with no significant differences in baseline angiographic characteristics. A majority of the patients (79%-83%) had multivessel disease, and about three-fourths had complex lesions.

The primary end point, in-stent late lumen loss at 1 year, was 0.17 mm for BP DES, 0.23 mm for Cypher, and 0.47 mm for PF DES. Compared with the Cypher, the results demonstrated noninferiority for the BP DES but not for the PF DES, Dr. Mehilli reported.

Drug-Eluting Stent Thrombosis Rate Suggests Acceleration Over Time

VIENNA — The incidence of stent thrombosis following placement of drug-eluting coronary stents suggested a possibly rising, curvilinear incidence during 3 years of follow-up of more than 5,000 patients.

In addition, almost half of the stent thromboses that occurred a year or more after stent placement happened while patients were still on dual antiplatelet therapy, said Dr. Gregory J. Mishkel said while presenting a poster at the annual congress of the European Society of Cardiology.

The finding “calls into question the necessity of clopidogrel continuation beyond the current prescribed recommendations” of 1 year, said Dr. Mishkel, co-director of the coronary catheterization laboratory at the Prairie Heart Institute at St. John’s Hospital in Springfield, Ill., and his associates in their poster.

The review included 5,342 patients at Prairie Heart who received their first DES

during May 2003–December 2006. Follow-up data on stent thrombosis was available for 5,173 (97%) of the patients; the average duration of follow-up was 1.8 years. During follow-up, 50 patients had a definite stent thrombosis, 13 had a probable event, and 54 had a possible stent thrombosis. Among the 50 definite thromboses, 34 (68%) occurred a year or more after placement; and of those, 15 (44%) occurred while the patients were still on dual antiplatelet therapy.

Rates of angiographic restenosis were 9.0% for the BP DES, 10.8% for the Cypher, and 16.9% for PF DES. Clinical restenosis (target lesion revascularization) rates were 5.9%, 7.9%, and 12.9%, respectively, all nonsignificant differences, compared with Cypher. Death or myocardial infarction occurred in 2.5% with BP DES, 3.5% with Cypher, and 4.0% with PF DES, while death rates were identical (2.5%) in each of the groups.

Definite/probable/possible stent thrombosis (Academic Research Consortium definition) occurred in 1.0% of the BP DES group, 2.0% with Cypher, and 1.5% of the PF DES recipients, also not significantly different. The three types of DES did not differ in terms of their safety profile at 1 year, Dr. Mehilli reported.

In a critical appraisal of ISAR-TEST 3, Dr. Jeffrey J. Popma called it “an important study” because “Reduction in intimal hyperplasia will not simply be enough as we move forward with our [DES] programs. We’re looking for new stents that have rapid endothelialization, less inflammation, and a reduction in the requirement for antiplatelet therapy, and these two agents may do that.”

The bioresorbable polymer might result in less very late stent thrombosis, while the microporous surface would possibly produce more rapid endothelialization, noted Dr. Popma, director of invasive cardiovascular services at Caritas Christi Health Care System, St. Elizabeth Research Center, Harvard Medical School, Boston.

However, he questioned whether “in-stent” late loss was the right primary study end point. While it is the best measure for the degree of intimal hyperplasia within the stent, it has no implications for endothelialization and healing. In-segment follow-up percent diameter stenosis would be a better predictor of clinical events, he said.

Drug-Eluting Stent Thrombosis Rate Suggests Acceleration Over Time

VIENNA — The incidence of stent thrombosis following placement of drug-eluting coronary stents suggested a possibly rising, curvilinear incidence during 3 years of follow-up of more than 5,000 patients.

In addition, almost half of the stent thromboses that occurred a year or more after stent placement happened while patients were still on dual antiplatelet therapy, said Dr. Gregory J. Mishkel said while presenting a poster at the annual congress of the European Society of Cardiology.

The finding “calls into question the necessity of clopidogrel continuation beyond the current prescribed recommendations” of 1 year, said Dr. Mishkel, co-director of the coronary catheterization laboratory at the Prairie Heart Institute at St. John’s Hospital in Springfield, Ill., and his associates in their poster.

The review included 5,342 patients at Prairie Heart who received their first DES

—Mitchel L. Zoler