BRIEF SUMMARY

ADENOSCAN®
adenosine injection

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 reflux 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 PCO_2 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 Hospira Inc.
Lake Forest, IL 60045 USA

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NEW & APPROVED

Remicade, Xact Carotid Stent

BY ELIZABETH MECHCATIE, SENIOR WRITER

Remicade
(infliximab, Centocor, Johnson & Johnson)

A tumor necrosis factor–α (TNF-α) blocking agent for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating steroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The first biologic approved for ulcerative colitis. Also approved for rheumatoid arthritis (1999), ankylosing spondylitis (2004), and psoriatic arthritis (May 2005).

Recommended Dosage: Administered in an intravenous infusion at a dose of 5 mg/kg at 0, 2, and 6 weeks (induction); and every 8 weeks thereafter (maintenance).

Special Considerations: The risk of serious infections is increased with Remicade. Lymphoma rates in treated patients have been greater than expected in the general population. The safety profile in the two trials that led to this approval so far appears to be consistent with the experience in rheumatoid arthritis and Crohn's, said William J. Sandborn, M.D., the lead investigator in one trial. Estimated annual cost is $15,000-$17,000, according to a Centocor spokesperson.

Comment: In the two studies of 728 patients with moderately to severely active ulcerative colitis who were not responding to other treatments, including steroids and immunosuppressives, the rates of clinical responses, sustained clinical responses, clinical remissions, and mucosal healing were significantly greater in the Remicade group at 30 weeks. More patients on Remicade discontinued prednisone (22% and 23%) than did those on placebo (10% and 3%).

"Response, remission, and mucosal healing occurred early," and responses seen at 8 weeks were sustained out to 30 weeks, said Dr. Sandborn, director of the inflammatory bowel disease clinical research unit at Mayo Medical Center, Rochester, Minn. The 54-week data from one trial will be available later this year.

Although the reason for the drug's clinical effect is not entirely clear, it is known that TNF levels in the intestinal wall, stool, and blood are elevated in patients with Crohn's disease and those with ulcerative colitis, he said.

Dr. Sandborn performs Centocor-funded research and is a consultant to the company.

Xact Carotid Stent
(Abbott Laboratories)

A carotid stent system approved for use with an embolic protection system, for patients with carotid artery disease who are at high risk for carotid endarterectomy and who meet certain criteria. The second carotid stent system to be approved.

Recommended Usage: Self-expanding nitinol stent, used with an embolic protection filter to capture emboli during the stenting procedure.

Special Considerations: Used in symptomatic patients with 50% or more carotid stenosis on ultrasound or angiography, or in asymptomatic patients with 80% or more stenosis, located between the origin of the common carotid artery and the intracranial segment of the internal carotid artery, according to the FDA. Contraindications include lesions in the ostium of the carotid artery and patients who cannot take anticoagulants or antiplatelet therapy or who have uncorrected bleeding disorders.

Comment: In a prospective, nonrandomized study of 305 patients in the United States and Australia, treatment of the target lesion was considered successful in 295 patients (97%), and at 30 days "overall procedural success" was reported in 269 patients (88%). Almost 93% had not experienced a major adverse event (death, stroke, or MI) at 30 days, one of the primary end points.

At 12 months, 99% of patients had not required a repeat vascularization, and restenosis was demonstrated in nearly 5% at 6 months after the procedure and 4% at 12 months after the procedure, according to the FDA. Within 30 days of the procedure, there were three deaths, all stroke-related. The company has agreed to conduct postmarketing studies, including one that will evaluate safety and effectiveness of the stent for 3 years after implantation in at least 305 patients.

Better Prophylaxis Against Upper GI Bleeding Needed Post Stenting

CHICAGO — Patients with coronory artery stents may not be getting the protection they need against the risk of upper GI bleeding due to antiplatelet therapy, according to a poster presented at the annual Digestive Disease Week.

In a chart review of 636 randomly selected patients who received cardiovascular stents, most also received aspirin before (n = 459) and/or after (n = 619) stent placement, which increased their risk of peptic ulcer–related bleeding, according to Steven Chang, M.D., and his colleagues.

After stenting, however, only 155 (24%) were prescribed a proton pump inhibitor; 14 (2%) were prescribed an H2-receptor antagonist; and 1 patient was prescribed sucralfate, reported Dr. Chang, who is a consultant to Santarus, a manufacturer of omeprazole. Outcomes data on GI bleeding were not available in the study.

—Kathleen Louden

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