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.
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47101/Revised: April 2005

Bupropion Not as Effective Outside of Clinical Trials

BY DAMIAN McNAMARA
Miami Bureau

NEW ORLEANS — Low-income smokers prescribed bupropion in primary care settings are less successful with smoking cessation than participants in controlled trials, according to a study presented at the annual conference of the Society of Teachers of Family Medicine.

Multicenter trials indicate that sustained-release bupropion helps 44% quit at 7 weeks, compared with 19% taking a placebo (N. Engl. J. Med. 1997; 337:1195-202) and 58% of cigarette smokers quit at 9 weeks, compared with 16% taking a placebo (N. Engl. J. Med. 1999;340:685-91).

The effectiveness of bupropion in a real clinical setting was less than half of what has been previously reported in highly controlled trials.

But participants in those bupropion trials did not reflect the patient population in Fresno County, according to Evelyn Fang, M.D. The county has a 23% poverty rate (vs. 14% for California), a high rate of stroke and heart disease, and an increasing rate of lung cancer deaths.

Physicians at one family medicine clinic and two internal medicine clinics associated with the University of California, San Francisco, Fresno campus, screened and referred patients to Dr. Fang and her associates. The researchers enrolled 72 participants over 3 months from the University of California, San Francisco, Fresno residency-affiliated training sites.

Dr. Fang, who is no longer with the university, was a clinical instructor in medicine when the study was conducted. John Zweifler, M.D., also of the University of California, San Francisco, Fresno, presented the study at the meeting.

Participants received a free 30-day supply of bupropion with one refill. They took one pill every day for 3 days, then increased to two pills daily, and were advised to stop smoking after 7 days.

The researchers surveyed participants by telephone at 30 days and 60 days. A total of 57 patients completed the follow-up and were studied further.

The mean age was 47 years and 65% were female. The group was 61% Caucasian, 19% Hispanic, 18% African American, and 2% Asian.

Participants reported a median of two previous attempts to quit smoking and a median of 30 years of cigarette smoking. A total of 17% stopped smoking at 3 months, as did 18% at 6 months.

Sustained-release bupropion may help low-income smokers in real clinical settings quit smoking, Dr. Zweifler, M.D., said, but the effect was less than half of what has been previously reported in highly controlled trials of more motivated patients.

Limitations of the study include the sample size and the lack of a control group. ■

Selective Nicotinic Receptor Partial Agonist May Be Cessation Advance

ORLANDO, FLA. — Varenicline, a first-of-its-kind selective nicotinic receptor partial agonist, has racked up unprecedented smoking-cessation success rates in a pair of phase II clinical trials, Cheryl A. Oncken, M.D., reported at the annual meeting of the American College of Cardiology.

Based on these extremely encouraging albeit short-term results, multiple yearlong phase III trials are underway using varenicline at 1 mg twice daily, a Pfizer spokesperson told this newspaper.

The two phase II placebo-controlled studies totaled 1,253 smokers. In one 6-week study, 48% of participants assigned to 1 mg of varenicline twice daily quit smoking for a 28-day period as determined by review of daily smoking diaries, compared with 37% on 1 mg/day of the drug, 33% on 150 mg of bupropion twice daily, 29% on 0.3 mg/day of varenicline, and 17% on placebo, said Dr. Oncken of the University of Connecticut, Farmington.

In the other study, which lasted 12 weeks, 51% of patients on 1 mg of varenicline twice daily abstained from smoking during weeks 9-12 as confirmed by carbon monoxide testing. This was also the case for 45% of those randomized to 0.5 mg of the drug twice daily and for 12% of the placebo group. The adjusted odds ratios for abstinence were 6.1 and 7.8 for 0.5 and 1 mg of varenicline twice daily, respectively, compared with placebo.

The most common varenicline-related side effect was transient mild to moderate nausea. Tolerability compared favorably to placebo in both studies. It also compared favorably to bupropion—a drug with a Food and Drug Administration indication for smoking cessation—in the one comparative trial where it was used, with discontinuation due to adverse events occurring in 11% of patients in the high-dose varenicline group and 16% of those on bupropion. No varenicline-related safety issues arose during monitoring of laboratory tests and ECGs.

Nicotine dependence in smokers is mediated via the neuronal $\alpha 4\ \beta 2$ nicotinic receptor. Varenicline is believed to act by blocking nicotine binding to the receptor during smoking, thereby interfering with smoking's extremely potent reinforcement and reward effects, Dr. Oncken explained.

Her investigations were sponsored by Pfizer Global Research and Development.

—Bruce Jancin