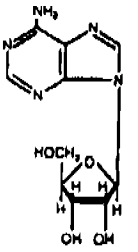
Fujisawa

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 and has the following structural formula:



$C_{10}H_{13}N_5O_4$ 267.24

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, nonpyrogenic 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.

CLINICAL PHARMACOLOGY:

Mechanism of Action
Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A_1 and A_2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A_2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since Adenoscan significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Adenoscan causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e., a greater difference is seen after Adenoscan between areas served by normal and areas served by stenotic vessels than is seen prior to Adenoscan.

Hemodynamics
Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A_1-receptor agonism, and produces peripheral vasodilation, presumably due to A_2-receptor agonism. The net effect of Adenoscan in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Pharmacokinetics
Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m and V_{max} than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As Adenoscan requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

Clinical Trials
In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 86.6% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (≥50% reduction in the luminal diameter of at least one major vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of

ADENOSCAN®
adenosine injection

patients with negative angiograms) was 64% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 58% to 78% and for specificity were 37% to 71%.

Intracoronary Doppler flow catheter studies have demonstrated that a dose of intravenous Adenoscan of 140 (mcg/kg/min produces maximum coronary hyperemia (relative to intracoronary papaverine) in approximately 95% of cases within two to three minutes of the onset of the infusion. Coronary blood flow velocity returns to basal levels within one to two minutes of discontinuing the Adenoscan infusion.

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 (adenosine injection) 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 non-fatal 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 (adenosine injection) 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 (2.8%), second-degree (2.8%) 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 (adenosine injection) 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 (adenosine injection) 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 (adenosine injection) 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,

Second-degree AV block	3%
Paresthesia	2%
Hypotension	2%
Nervousness	2%
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.

vial, packaged individually and in packages of ten.

Store at controlled room temperature 15°-30°C (59°-86°F).
Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming in room temperature. The solution must be clear at the time of use.
Contains no preservative. Discard unused portion.

Rx only

Manufactured for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015

50-6295-R3
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