

Adenosine Injection, USP 3 mg/mL

Antiarrhythmic

ACTION AND CLINICAL PHARMACOLOGY

Adenosine is an endogenous nucleoside occurring in all cells of the body. When injected intravenously, adenosine slows atrioventricular (AV) nodal conduction, can interrupt the reentry pathways through the AV node and can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardia (PSVT), including PSVT associated with Wolff-Parkinson-White syndrome.

Adenosine is antagonized competitively by methylxanthines such as caffeine and theophylline, and potentiated by blockers of nucleoside transport such as dipyridamole. Adenosine is not blocked by atropine.

In controlled clinical trials, cumulative 60% and 92% of patients converted to normal sinus rhythm within one minute after 6 mg and 12 mg bolus doses of adenosine, respectively. In other controlled clinical trials with bolus doses of 3, 6, 9, and 12 mg, some patients with paroxysmal supraventricular tachycardia converted to normal sinus rhythm on 3 mg of adenosine. Reports in the medical literature indicate success in treating PSVT in pediatric patients (including newborns) with adenosine in doses equivalent by weight to those used in adults.

Adenosine is not effective in converting rhythms other than PSVT, such as atrial flutter, atrial fibrillation, or ventricular tachycardia to normal sinus rhythm.

Hemodynamics

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. The intravenous bolus dose of 6 or 12 mg adenosine usually has no systemic hemodynamic effects. When larger doses are given by infusion, adenosine decreases blood pressure by decreasing peripheral resistance.

Pharmacokinetics

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells, with a half-life of less than 10 seconds. 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. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. Inosine formed by deamination of adenosine can leave the cell intact or can be metabolized to hypoxanthine, xanthine, and ultimately uric acid.

Since neither the kidney nor the liver are required for the metabolism or elimination of adenosine, the activity of adenosine should be unaffected by hepatic or renal insufficiency.

INDICATIONS AND CLINICAL USE

Adenosine Injection, USP is indicated for the conversion to sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including that associated with accessory bypass tracts (Wolff-Parkinson-White syndrome). When clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver) should be attempted prior to adenosine administration.

Adenosine is indicated to aid in the diagnosis of broad or narrow complex supraventricular tachycardia. Although adenosine is not effective in converting atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the transient atrioventricular nodal block produced helps diagnosis of atrial activity.

It is essential to ascertain that adenosine actually reaches the systemic circulation (see **DOSAGE AND ADMINISTRATION**).

Adenosine **does not** convert atrial flutter, atrial fibrillation or ventricular tachycardia to normal sinus rhythm.

Adenosine should only be used with appropriate cardiac monitoring.

CONTRAINDICATIONS

Adenosine Injection, USP is contraindicated in:

- Second-, or third-degree AV block (except in patients with a functioning artificial pacemaker);
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker);
- Symptomatic bradycardia (except in patients with a functioning artificial pacemaker);
- Known hypersensitivity to adenosine.

WARNINGS

Heart Block

Adenosine exerts its effect by decreasing conduction through the AV node and may produce a short lasting first-, second-, or third-degree heart block. Appropriate therapy should be instituted as needed. Patients who develop high-level block on one dose of adenosine should not be given additional doses. Because of the very short half-life of adenosine (< 10 seconds), these effects are generally self-limiting.

Rarely, ventricular fibrillation/flutter has been reported following adenosine administration, including both resuscitated and fatal events. In most instances, these cases were associated with the concomitant use of digoxin, and **less frequently with digoxin and verapamil**. Adenosine should be used with caution in patients receiving digoxin **or digoxin and verapamil in combination**. Appropriate resuscitative measures should be available.

Patients with atrial fibrillation/flutter and an accessory bypass tract may develop increased conduction down the anomalous pathway.

Arrhythmias at Time of Conversion

At the time of conversion to normal sinus rhythm, a variety of new rhythms may appear on the electrocardiogram. They generally last only a few seconds without intervention, and may take the form of premature ventricular contractions, polymorphic ventricular tachycardia, torsades de pointes, atrial premature contractions, sinus bradycardia, sinus tachycardia, skipped beats, and varying degrees of AV nodal block. These arrhythmias and conduction disturbances were observed in about 55% of patients.

Asystole

Transient or prolonged episodes of asystole have been reported with fatal outcomes in some cases.

Bronchoconstriction

Adenosine has been administered to a limited number of patients with asthma, and serious exacerbation of their symptoms has been reported in some patients. Respiratory compromise has occurred during adenosine infusion in patients with chronic obstructive pulmonary disease (COPD). Therefore, the use of adenosine should be avoided in patients with COPD or asthma.

Adenosine therapy should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS

Use in Pregnancy

Adenosine is a substance naturally present in the body and therefore no fetal effects would be anticipated. However, since it is not known whether adenosine can cause fetal harm when administered to pregnant women, it should not be used during pregnancy unless potential benefits outweigh the potential risks to the fetus.

Use in Children

No controlled studies have been conducted in pediatric patients to establish the safety and efficacy of adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, open-label studies carried

out by independent investigators indicated that intravenous adenosine can be used safely in neonates, infants, children, and adolescents. (See **DOSAGE AND ADMINISTRATION, Pediatric Patients**.)

Use in Elderly

Clinical studies of adenosine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, adenosine in geriatric patients should be used with caution since this population may have a diminished cardiac function, nodal dysfunction, concomitant diseases or drug therapy that may alter hemodynamic function and produce severe bradycardia or AV block.

Drug Interactions

Cardioactive Drugs: Adenosine has been effectively administered in the presence of other cardioactive drugs, such as quinidine, beta-adrenergic blocking agents, calcium channel blocking agents, and angiotensin converting enzyme inhibitors, without any change in the adverse reaction profile. **Digoxin and verapamil use may be rarely associated with ventricular fibrillation when combined with adenosine** (see **WARNINGS**). Because of the synergistic depressant effects on the SA and AV nodes, adenosine should be used with caution in the presence of these agents.

Methylxanthines: The effects of adenosine are antagonized by methylxanthines (such as caffeine and theophylline). In the presence of methylxanthines, larger doses of adenosine may be required or adenosine may not be effective.

Dipyridamole: Adenosine effects are potentiated by dipyridamole. Thus, smaller doses of adenosine may be effective in the presence of dipyridamole.

Carbamazepine: Carbamazepine has been reported to increase the degree of heart block produced by other agents. Since the primary effect of adenosine is to decrease conduction through the AV node, higher degrees of heart block may be produced in the presence of carbamazepine.

ADVERSE REACTIONS

In controlled clinical trials, 268 patients received adenosine. One hundred and two patients (38%) experienced one or more adverse events. These adverse events appeared immediately after administration of adenosine and usually lasted less than one minute. The most common adverse reactions were: facial flushing (18%), dyspnea (12%), chest pressure (7%), and nausea (3%).

Cardiovascular Facial flushing (18%), headache (2%), sweating, palpitations, chest pain, and hypotension (less than 1%). A variety of arrhythmias and conduction disturbances were observed in about 55% of patients at the time of conversion to normal sinus rhythm.

Respiratory Shortness of breath/dyspnea (12%), chest pressure (7%), hyperventilation, and head pressure (less than 1%).

Central Nervous System Light-headedness (2%), dizziness, tingling in arms, numbness (1%), apprehension, blurred vision, burning sensation, heaviness in arms, and neck and back pain (less than 1%).

Gastrointestinal Nausea (3%) and metallic taste, tightness in throat, and pressure in groin (less than 1%).

The following adverse events have been reported from marketing experience with adenosine. Because these events are reported voluntarily from a population of uncertain size, and 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.

Cardiovascular Prolonged asystole, ventricular tachycardia, ventricular fibrillation, transient increase in blood pressure, bradycardia, atrial fibrillation, and torsades de pointes (see **WARNINGS** and **PRECAUTIONS**).

Respiratory Bronchospasm.

Central Nervous System Convulsions, grand mal and tonic clonic seizures.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No cases of overdosage associated with the use of adenosine have been reported. It is unlikely that the true overdosage will occur because adenosine has a short half-life (< 10 seconds) and because adenosine is dosed by a rapid bolus injection. If prolonged adverse events associated with the use of adenosine occur, treatment should be individualized and directed towards the specific event. To date, no patient has required administration of adenosine antagonists such as aminophylline to counteract adverse events associated with the use of adenosine.

In clinical studies on the use of adenosine as a diagnostic agent in imaging, less than 0.1% of the patients exposed to adenosine were described as having severe, prolonged adverse events. These prolonged adverse events were treated with aminophylline after discontinuation of the adenosine infusion. The usual concentration of aminophylline used was 1.25 mg/mL (125 mg in 100 mL) administered intravenously over five to six minutes. An additional 1.25 mg/mL (125 mg in 100 mL) can be administered, but clinical experience has demonstrated that this is rarely required.

DOSAGE AND ADMINISTRATION

Adenosine Injection, USP should only be used with appropriate cardiac monitoring.

Adenosine Injection should be given as a rapid bolus intravenous injection. To be certain the solution reaches the systemic circulation, it should be administered either directly into a peripheral vein or, if given into an i.v. line, it should be given as close to the patient as possible and followed by a rapid saline flush.

Adult Patients

The recommended intravenous doses for adults are as follows:

Initial dose: 6 mg administered as a rapid intravenous bolus given over a 1- to 2-second time period.

Additional doses: If the initial dose does not terminate supraventricular tachycardia within 1 - 2 minutes, 12 mg dose should be given as a rapid intravenous bolus. This 12 mg dose may be repeated a second time if required. Single bolus injections greater than 12 mg are not recommended.

Pediatric Patients

Pediatric patients with a body weight < 50 kg:

Initial dose: Give 0.05 - 0.10 mg/kg as a rapid intravenous bolus given either centrally or peripherally.

Additional doses: If conversion of PSVT does not occur within 1 - 2 minutes, additional bolus injections of adenosine can be administered at incrementally higher doses, increasing the amount given by 0.05 - 0.10 mg/kg. Follow each bolus with a saline flush. This process should be continued until sinus rhythm is established or up to a maximum dose of 0.3 mg/kg.

For pediatric patients who require single intravenous doses less than 0.6 mg (0.2 mL of 3 mg/mL solution), Adenosine Injection may be further diluted with normal saline to a final concentration range from 0.3 to 1.0 mg/mL in a suitable glass container as follows:

Desired Concentration (mg/mL)	Volume of Adenosine Injection, 3 mg/mL Required (mL)	Volume of Diluent Required (mL)	Final Volume of Diluted Solution (mL)
0.3	1	9	10
1.0	1	2	3

Diluted solutions should be used immediately. Discard unused portion.

As with all parenteral products, intravenous admixtures should be inspected for clarity of solutions, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Patient with a body weight ≥ 50 kg:

Administer the adult dose.

Single bolus injections greater than 12 mg are not recommended for adult or pediatric patients.

NOTE: Adenosine Injection should be inspected visually for particulate matter and discoloration prior to administration.

Adenosine Injection **should not** be refrigerated as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

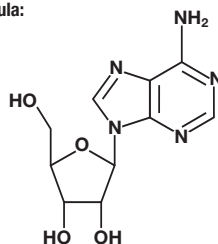
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Adenosine

Chemical Name: 6-amino-9-β-D-ribofuranosyl-9-H-purine; Adenine riboside

Structural Formula:



Molecular Weight: 267.2

Molecular Formula: C₁₀H₁₃N₅O₄

Description: Adenosine is a white crystalline powder. It is soluble in water (7 mg/mL at pH 7.0) and practically insoluble in alcohol. Solubility increases by warming and by lowering the pH. The melting point is 233 - 238°C.

Composition: Adenosine Injection, USP is a sterile solution for rapid bolus intravenous injection and is available in 6 mg/2 mL vials, 6 mg/2 mL prefilled syringes, and 12 mg/4 mL prefilled syringes. Each mL contains 3 mg adenosine and 9 mg Sodium Chloride in Water for Injection. The pH of the solution is between 4.5 and 7.5. **Adenosine Injection, USP does not contain preservatives, colours or additives.**

STABILITY AND STORAGE RECOMMENDATIONS

Adenosine Injection, USP should be stored at controlled room temperature (15 - 30°C). Single-use vials and syringes. Discard unused portion. **Do not refrigerate** as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

AVAILABILITY OF DOSAGE FORMS

Adenosine Injection, USP is supplied as a sterile nonpyrogenic solution in normal saline as single-dose vial or syringe.

Product Code:

- C605102 2 mL single-dose flip-top vials containing 6 mg adenosine/2 mL solution (3 mg/mL) in a package of 10.
- CP010102 6 mg in 2 mL (fill volume) BD Hypack® glass disposable syringes, in a package of 1.
- CP010104 12 mg in 4 mL (fill volume) BD Hypack® glass disposable syringes, in a package of 1.

Vial stoppers and syringe stoppers do not contain natural rubber latex.

Instructions for Syringe Use

The BD Hypack® syringe delivery system easily adapts to most peripheral line connection valves without the use of a needle. A BD Q-Syte™ or other adaptor is required for use with the CLAVE® system. A needle is not provided

with the Adenosine Injection, USP BD Hypack® syringe delivery system. Should you require the use of a needle to inject Adenosine Injection directly into a vein, the adaptable Luer Lock tip can accommodate an 18 or 20 gauge needle. Expel air from the syringe before use. Syringes and vials are intended for **single use only**. Any portion of the vial or syringe not used at once should be discarded. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken by hand. BD Hypack and Q-Syte are registered trademarks of Becton, Dickinson and Company. CLAVE is a registered trademark of ICU Medical Inc.

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