

1 **ADENOCARD® IV**

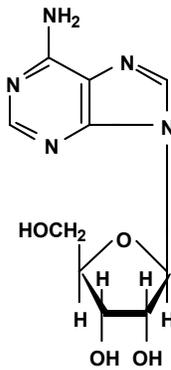
2 **(adenosine injection)**

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4 **For Rapid Bolus Intravenous Use**

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6 Revised: April 2005

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8 **DESCRIPTION:**

9 Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-  
10 amino-9-β-D-ribofuranosyl-9-H-purine and has the following structural formula:



22 **C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>**

23 **267.24**

24 Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in  
25 alcohol. Solubility increases by warming and lowering the pH. Adenosine is not chemically  
26 related to other antiarrhythmic drugs. Adenocard<sup>®</sup> (adenosine injection) is a sterile,  
27 nonpyrogenic solution for rapid bolus intravenous injection. Each mL contains 3 mg adenosine  
28 and 9 mg sodium chloride in Water for Injection. The pH of the solution is between 4.5 and 7.5.

29 The **Ansy<sup>®</sup>** plastic syringe is molded from a specially formulated polypropylene. Water  
30 permeates from inside the container at an extremely slow rate which will have an insignificant  
31 effect on solution concentration over the expected shelf life.

32 Solutions in contact with the plastic container may leach out certain chemical  
33 components from the plastic in very small amounts; however, biological testing was supportive  
34 of the safety of the syringe material.

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## **CLINICAL PHARMACOLOGY:**

### **Mechanism of Action**

38 Adenocard (adenosine injection) slows conduction time through the A-V node, can interrupt the  
39 reentry pathways through the A-V node, and can restore normal sinus rhythm in patients with  
40 paroxysmal supraventricular tachycardia (PSVT), including PSVT associated with Wolff-  
41 Parkinson-White Syndrome.

42 Adenocard is antagonized competitively by methylxanthines such as caffeine and  
43 theophylline, and potentiated by blockers of nucleoside transport such as dipyridamole.

44 Adenocard is not blocked by atropine.

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47 **Hemodynamics**

48 The intravenous bolus dose of 6 or 12 mg Adenocard (adenosine injection) usually has no  
49 systemic hemodynamic effects. When larger doses are given by infusion, adenosine decreases  
50 blood pressure by decreasing peripheral resistance.

51

52 **Pharmacokinetics**

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

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70 **Clinical Trial Results**

71 In controlled studies in the United States, bolus doses of 3, 6, 9, and 12 mg were studied. A  
72 cumulative 60% of patients with paroxysmal supraventricular tachycardia had converted to  
73 normal sinus rhythm within one minute after an intravenous bolus dose of 6 mg Adenocard  
74 (some converted on 3 mg and failures were given 6 mg), and a cumulative 92% converted after a  
75 bolus dose of 12 mg. Seven to sixteen percent of patients converted after 1-4 placebo bolus  
76 injection. Similar responses were seen in a variety of patient subsets, including those using or  
77 not using digoxin, those with Wolff-Parkinson-White Syndrome, males, females, blacks,  
78 Caucasians, and Hispanics.

79 Adenosine is not effective in converting rhythms other than PSVT, such as atrial flutter,  
80 atrial fibrillation, or ventricular tachycardia, to normal sinus rhythm. To date, such patients have  
81 not had adverse consequences following administration of adenosine.

82

83 **INDICATIONS AND USAGE:**

84 Intravenous Adenocard (adenosine injection) is indicated for the following.

85 Conversion to sinus rhythm of paroxysmal supraventricular tachycardia (PSVT),  
86 including that associated with accessory bypass tracts (Wolff-Parkinson-White Syndrome).

87 When clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver), should be  
88 attempted prior to Adenocard administration.

89 It is important to be sure the Adenocard solution actually reaches the systemic circulation  
90 (see **DOSAGE AND ADMINISTRATION**).

91 Adenocard does not convert atrial flutter, atrial fibrillation, or ventricular tachycardia to  
92 normal sinus rhythm. In the presence of atrial flutter or atrial fibrillation, a transient modes  
93 tslowing of ventricular response may occur immediately following Adenocard administration.

94

#### 95 **CONTRAINDICATIONS:**

96 Intravenous Adenocard (adenosine injection) is contraindicated in:

- 97 1. Second- or third-degree A-V block (except in patients with a functioning artificial  
98 pacemaker).
- 99 2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in  
100 patients with a functioning artificial pacemaker).
- 101 3. Known hypersensitivity to adenosine.

102

#### 103 **WARNINGS:**

##### 104 **Heart Block**

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

110 Transient or prolonged episodes of asystole have been reported with fatal outcomes in  
111 some cases. Rarely, ventricular fibrillation has been reported following Adenocard  
112 administration, including both resuscitated and fatal events. In most instances, these cases were  
113 associated with the concomitant use of digoxin and, less frequently with digoxin and verapamil.

114 Although no causal relationship or drug-drug interaction has been established, Adenocard should  
115 be used with caution in patients receiving digoxin or digoxin and verapamil in combination.

116 Appropriate resuscitative measures should be available.

117

### 118 **Arrhythmias at Time of Conversion**

119 At the time of conversion to normal sinus rhythm, a variety of new rhythms may appear on the  
120 electrocardiogram. They generally last only a few seconds without intervention, and may take  
121 the form of premature ventricular contractions, atrial premature contractions, sinus bradycardia,  
122 sinus tachycardia, skipped beats, and varying degrees of A-V nodal block. Such findings were  
123 seen in 55% of patients.

124

### 125 **Bronchoconstriction**

126 Adenocard (adenosine injection) is a respiratory stimulant (probably through activation of  
127 carotid body chemoreceptors) and intravenous administration in man has been shown to increase  
128 minute ventilation ( $V_e$ ) and reduce arterial  $PCO_2$  causing respiratory alkalosis.

129 Adenosine administered by inhalation has been reported to cause bronchoconstriction in  
130 asthmatic patients, presumably due to mast cell degranulation and histamine release. These  
131 effects have not been observed in normal subjects. Adenocard has been administered to a limited  
132 number of patients with asthma and mild to moderate exacerbation of their symptoms has been  
133 reported. Respiratory compromise has occurred during adenosine infusion in patients with  
134 obstructive pulmonary disease. Adenocard should be used with caution in patients with  
135 obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis,

136 etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma).  
137 Adenocard should be discontinued in any patient who develops severe respiratory difficulties.

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## **PRECAUTIONS:**

### **141 Drug Interactions**

142 Intravenous Adenocard (adenosine injection) has been effectively administered in the presence  
143 of other cardioactive drugs, such as quinidine, beta-adrenergic blocking agents, calcium channel  
144 blocking agents, and angiotensin converting enzyme inhibitors, without any change in the  
145 adverse reaction profile. Digoxin and verapamil use may be rarely associated with ventricular  
146 fibrillation when combined with Adenocard (see **WARNINGS**). Because of the potential for  
147 additive or synergistic depressant effects on the SA and AV nodes, however, Adenocard should  
148 be used with caution in the presence of these agents. The use of Adenocard in patients receiving  
149 digitalis may be rarely associated with ventricular fibrillation (see **WARNINGS**).

150 The effects of adenosine are antagonized by methylxanthines such as caffeine and  
151 theophylline. In the presence of these methylxanthines, larger doses of adenosine may be  
152 required or adenosine may not be effective. Adenosine effects are potentiated by dipyridamole.

153 Thus, smaller doses of adenosine may be effective in the presence of dipyridamole.

154 Carbamazepine has been reported to increase the degree of heart block produced by other agents.

155 As the primary effect of adenosine is to decrease conduction through the A-V node, higher  
156 degrees of heart block may be produced in the presence of carbamazepine.

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158

159 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

160 Studies in animals have not been performed to evaluate the carcinogenic potential of Adenocard  
161 (adenosine injection). Adenosine was negative for genotoxic potential in the Salmonella (Ames  
162 Test) and mammalian Microsome Assay.

163 Adenosine, however, like other nucleosides at millimolar concentrations present for  
164 several doubling times of cells in culture, is known to produce a variety of chromosomal  
165 alterations. Fertility studies in animals have not been conducted with adenosine.

166

167 **Pregnancy Category C**

168 Animal reproduction studies have not been conducted with adenosine; nor have studies been  
169 performed in pregnant women. As adenosine is a naturally occurring material, widely dispersed  
170 throughout the body, no fetal effects would be anticipated. However, since it is not known  
171 whether Adenocard can cause fetal harm when administered to pregnant women, Adenocard  
172 should be used during pregnancy only if clearly needed.

173

174 **Pediatric Use**

175 No controlled studies have been conducted in pediatric patients to establish the safety and  
176 efficacy of Adenocard for the conversion of paroxysmal supraventricular tachycardia (PSVT).  
177 However, intravenous adenosine has been used for the treatment of PSVT in neonates, infants,  
178 children and adolescents (see **DOSAGE AND ADMINISTRATION**).

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182 **Geriatric Use**

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

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**ADVERSE REACTIONS:**

191 The following reactions were reported with intravenous Adenocard (adenosine injection) used in  
192 controlled U.S. clinical trials. The placebo group had less than 1% rate of all of these reactions.

193

194 **Cardiovascular** Facial flushing (18%), headache (2%), sweating, palpitations, chest pain,  
195 hypotension (less than 1%).

196

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

199

200 **Central Nervous System** Lightheadedness (2%), dizziness, tingling in arms, numbness (1%),  
201 apprehension, blurred vision, burning sensation, heaviness in arms, neck  
202 and back pain (less than 1%).

203

204 **Gastrointestinal** Nausea (3%), metallic taste, tightness in throat, pressure in groin (less than  
205 1%).

206

207 **Post Marketing Experience** (see **WARNINGS**)

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209 The following adverse events have been reported from marketing experience with Adenocard.

210 Because these events are reported voluntarily from a population of uncertain size, are associated

211 with concomitant diseases and multiple drug therapies and surgical procedures, it is not always

212 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

213 Decisions to include these events in labeling are typically based on one or more of the following

214 factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal

215 connection to the drug, or a combination of these factors.

216

217 **Cardiovascular**

218 Prolonged asystole, ventricular tachycardia, ventricular fibrillation, transient increase in blood

219 pressure, bradycardia, atrial fibrillation, and Torsade de Pointes

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221 **Respiratory**

222 Bronchospasm

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224 **Central Nervous System**

225 Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness.

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**OVERDOSAGE:**

The half-life of Adenocard (adenosine injection) is less than 10 seconds. Thus, adverse effects are generally rapidly self-limiting. Treatment of any prolonged adverse effects should be individualized and be directed toward the specific effect. Methylxanthines, such as caffeine and theophylline, are competitive antagonists of adenosine.

**DOSAGE AND ADMINISTRATION:**

For rapid bolus intravenous use only.

**Adenocard (adenosine injection) should be given as a rapid bolus by the peripheral intravenous route. To be certain the solution reaches the systemic circulation, it should be administered either directly into a vein or, if given into an IV line, it should be given as close to the patient as possible and followed by a rapid saline flush.**

**Adult Patients**

The dose recommendation is based on clinical studies with peripheral venous bolus dosing. Central venous (CVP or other) administration of Adenocard has not been systematically studied.

The recommended intravenous doses for adults are as follows:

**Initial dose:** 6 mg given as a rapid intravenous bolus (administered over a 1-2 second period).  
**Repeat administration:** If the first dose does not result in elimination of the supraventricular tachycardia within 1-2 minutes, 12 mg should be given as a rapid intravenous bolus. This 12 mg dose may be repeated a second time if required.

250 **Pediatric Patients**

251 The dosages used in neonates, infants, children and adolescents were equivalent to those  
252 administered to adults on a weight basis.

253

254 **Pediatric Patients with a Body Weight < 50 kg:**

255 **Initial dose:** Give 0.05 to 0.1 mg/kg as a rapid IV bolus given either centrally or peripherally.

256 A saline flush should follow.

257 **Repeat administration:** If conversion of PSVT does not occur within 1-2 minutes, additional  
258 bolus injections of adenosine can be administered at incrementally higher doses, increasing the  
259 amount given by 0.05 to 0.1 mg/kg. Follow each bolus with a saline flush. This process should  
260 continue until sinus rhythm is established or a maximum single dose of 0.3 mg/kg is used.

261

262 **Pediatric Patients with a Body Weight ≥ 50 kg:**

263 Administer the adult dose.

264 **Doses greater than 12 mg are not recommended for adult and pediatric patients.**

265 NOTE: Parenteral drug products should be inspected visually for particulate matter and  
266 discoloration prior to administration.

267

268 **HOW SUPPLIED:**

269 Adenocard<sup>®</sup> (adenosine injection) is supplied as a sterile non-pyrogenic solution in normal  
270 saline.

271 NDC 0469-8234-12 Product Code 8234-12

272 6 mg/2 mL (3 mg/mL) in 2 mL (fill volume) **Ansyr**<sup>®</sup> plastic disposable syringe, in a package of  
273 ten.

274 NDC 0469-8234-14 Product Code 8234-14

275 12 mg/4 mL (3 mg/mL) in 4 mL (fill volume) **Ansyr**<sup>®</sup> plastic disposable syringe, in a package of  
276 ten.

277

278 Store at controlled room temperature 15°-30°C (59°-86°F).

279 **DO NOT REFRIGERATE** as crystallization may occur. If crystallization has occurred,  
280 dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

281 Contains no preservatives. Discard unused portion.

282 May require needle or blunt. To prevent needle-stick injuries, needles should not be  
283 recapped, purposely bent or broken by hand.

284

285 **Rx Only**

286

287 **REFERENCE:**

288 1. Paul T, Pfammatter. J-P. Adenosine: an effective and safe antiarrhythmic drug in pediatrics.

289 Pediatric Cardiology 1997; 18:118-126.

290

291 **Ansyr**<sup>®</sup> is a registered trademark of Hospira, Inc.

292

293 **Marketed by:**

294 Astellas Pharma US, Inc.

295 Deerfield, IL 60015

296

297 **Manufactured by:**

298 Hospira, Inc., Lake Forest, IL 60045 USA

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300 Revised: April 2005

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