



ADENOCAINE® INFORMATION

Adenocaine is the registered trademark of Hibernation Therapeutics Global, Ltd for a patented compounded solution comprised of adenosine, lidocaine and adjunctive ions. US Patent Numbers 6,955,814, 7,223,413 and 7,749,522 titled "Organ Arrest, Protection & Preservation" and additional patents pending.

PHARMACOLOGY AND GENERAL INFORMATION:

Adenosine is an endogenous nucleoside occurring in all cells of the body and exerts its actions primarily by binding to cell surface adenosine receptors (A1, A2a, A2b and A3).^{2,7} Lidocaine is a local anesthetic and a Class 1B antiarrhythmic agent, and it exerts its effects largely by blocking and/or modulating sodium (Na⁺) fast channels.^{2,7} Both drugs have been shown to stabilize and polarize the cell membrane and down-regulate excitable tissue. Both drugs possess anti-arrhythmic, anti-ischemic and anti-inflammatory properties¹ and dilate the coronary arteries. Basic science studies have demonstrated that both drugs in the Adenocaine® Cardioplegia Solution act in synergism to produce faster cardioplegic arrest times, greater anti-inflammatory effects and confer greater protection and preservation qualities on the heart than adenosine and lidocaine alone.^{1,3-7, 9,10} Adenocaine® cardioplegia is absorbed systemically (unless specifically harvested from the coronary sinus) and the pharmacokinetics are consistent for that of each component (adenosine, lidocaine, and magnesium) separately.

Clinical Use: Adenocaine® Solution is used to maintain heart arrest during cardiac surgery and for reanimation prior to cross clamp removal. According to reported human use,^{7,11,12} Adenocaine® cardioplegia and reanimation has been shown to be beneficial when the patient's blood potassium levels are kept in the normal physiological range (3.7 to 5.5 mEq/L)⁹. Based on these publications, low potassium Adenocaine® cardioplegia and reanimation may find utility in patients who cannot tolerate swings in plasma K⁺ such as those with renal disease or on dialysis.

ADENOCAINE® COMPOUNDING

Central Admixture Pharmacy Services Inc. (CAPS®) (a B. Braun company) is a network of state licensed, FDA registered compounding pharmacies. CAPS meets or exceeds USP 797 guidelines for pharmacy admixture.

Each Adenocaine® 40mL syringe contains:

40mg Adenosine, 40mg Lidocaine, 4g Magnesium Sulfate, 16.7mL 0.9% Sodium Chloride

Shelf Life: Each Adenocaine® cardioplegia syringe has an Expiration Date of 45 days from the date it is compounded.

Storage Recommendation: Store at Room Temperature (23° to 27° C). Do Not Freeze.

Sample Adenocaine® Cardioplegia Solution Label:



The formulation and use of the patented Adenocaine® Cardioplegia Solution is exclusively licensed to Central Admixture Pharmacy Services, Inc. (CAPS®) for compounding in the U.S. The patented formulation can be ordered by prescription directly from a local CAPS facility. For more information, please call (800) 853-6498 or visit www.capspharmacy.com/Adenocaine

STABILITY, STORAGE AND TESTING

CAPS contracted with an FDA registered independent test laboratory to design and perform stability testing. CAPS prepared an admixture solution of Adenosine® Injection, Lidocaine Injection, Magnesium Sulfate Injection and Sodium Chloride Injection for use as Adenocaine Cardioplegia Solution. The product was compounded under aseptic condition and within ISO Class 5 environment using only sterile ingredients, components and products. The admixture solutions are typically filled in a syringe with a fill volume of 40-mL and stored at controlled room temperature after production.

Independent stability studies for the Adenocaine® Cardioplegia Solution were based on USP Methods for Adenosine Injection, Lidocaine Injection, Magnesium Sulfate Injection, and Sodium Chloride Injection. The data established the shelf-life of Adenocaine® Cardioplegia Solution at three different storage conditions, refrigerated (2° to 8° C), 25°C (23° to 27° C), and under ambient laboratory light (approximately 150 to 240 foot candles) and controlled room temperature (20°C to 25°C with allowable excursions per USP) conditions. The stability of the product was evaluated based on the acceptable chemistry and microbiological data for the study. All the results met the specifications per protocol.

FDA Approved Clinical Indications for Adenosine, Lidocaine and Magnesium Sulfate

ADENOSINE

Adenosine is an FDA approved antiarrhythmic agent.

Uses/Indications: Supraventricular tachycardia

Contraindications: 2nd or 3rd degree A-V block, sick sinus syndrome (unless pacemaker in situ); asthma.

Precautions: Atrial fibrillation or flutter with accessory pathway; prolonged QT interval; recent heart transplant (< 1 yr); obstructive lung disease; pregnancy, lactation, children

Adverse Reactions: Facial flush; headache; chest pressure; dyspnoea; light-headedness; nausea; severe bradycardia; ventricular excitability; others,

For more information see the Official FDA information on adenosine

<http://www.drugs.com/pro/adenosine.html>

LIDOCAINE

Lidocaine (lignocaine) is an FDA approved antiarrhythmic agent.

Uses/Indications: Treatment or prophylaxis of life threatening ventricular arrhythmias

Contraindications: Stokes-Adams syndrome; severe heart block; supraventricular arrhythmias; sensitivity to amide local anaesthetics; concomitant drugs

Precautions: Severe shock, bradycardia, hypovolemia, cardiac conduction disturbances, severe digitalis intoxication; hypokalemia, acid-base disturbances; hepatic or renal impairment; CHF, chronic cardiac output elevation; malignant hyperthermia (family history of); cross sensitivity; acutely ill patients; elderly, debilitated; pregnancy, children

Adverse Reactions: CNS, cardiovascular disturbances; others, see MIMs.

Drug Interactions: Antiarrhythmics, amiodarone, beta-blockers, cimetidine, anticonvulsants, inhalation anesthetics, muscle relaxants, alcohol.

For more information see the Official FDA information on lidocaine

<http://www.drugs.com/pro/lidocaine.html>

MAGNESIUM SULFATE

For more information see the Official FDA information on Magnesium Sulfate

<http://www.drugs.com/pro/magnesium-sulfate.html>

Clinical Studies

- **Safety Study:** Jin and colleagues reported that Adenocaine® with moderate potassium was safe in 134 pediatric patients undergoing correction of ventricular septal defect.¹¹ Possible cardioprotection benefits were: 1) a reduced use of inotropes, 2) a significantly lower release of troponin I following surgery, and 3) a day less in hospital.¹¹
- **High Risk Case Study:** Adenocaine® cardioplegia was used in blood cardioplegia to arrest and protect the heart on an extremely high-risk 4X redo patient with infective endocarditis. This patient was on cardiopulmonary bypass (CPB) for 9.8 hours with a total cross-clamp time of 7 hours using Adenocaine®.¹²

LIST OF PUBLICATIONS ON ADENOCAINE® COMPOUND

1. **Shi WW., Jiang R., Dobson GP. and Vinten-Johansen J.** *The novel non-depolarizing, normokalemic cardioplegia formulation adenosine-lidocaine (Adenocaine) exerts superior antineutrophil effects by synergistic actions of its components.* **J Thorac Cardiovasc Surg. 2011; (In Press)**
2. **Dobson GP. Vinten Johansen J.** *Hyperkalemic cardioplegia: the end of an era?*
Review Article: Eur. J Cardiovasc Surg. 2010; (In submission)
3. **Rudd D. and Dobson GP.** *Eight hours of cold static storage with adenosine and lidocaine (adenocaine) heart preservation solutions: towards therapeutic suspended animation.* **J. Thorac Cardiovasc. Surg. 2011; (In press)**
4. **Letson HL., Dobson GP.** *Ultra-Small Intravenous Bolus of 7.5% NaCl/Mg²⁺ With Adenosine and Lidocaine Improves Early Resuscitation Outcome in the Rat After Severe Hemorrhagic Shock In Vivo.*
J Trauma. 2011; (In press) Jan 18. [Epub ahead of print]
5. **Letson HL., Dobson GP.** *Small Volume 7.5% NaCl With 6% Dextran-70 or 6% and 10% Hetastarch Are Associated With Arrhythmias and Death After 60 Minutes of Severe Hemorrhagic Shock in the Rat In Vivo.*
J Trauma. 2011; 70 (6):1444-52
6. **Rudd DM. and Dobson GP.** *Early reperfusion with warm, polarizing adenosine-lidocaine improves functional recovery following 6 hours of cold static storage* **J Thorac Cardiovasc Surg. 2011; 141(4):1044-55**
7. **Dobson GP.** *Membrane Polarity: A Target for Myocardial Protection and Reduced Inflammation in Adult and Pediatric Cardiothoracic Surgery (Editorial)* **J Thorac Cardiovasc. Surg. 2010; 140(6):1213-1217**
8. **Hammon J.** *Why Change? (Commentary)* **J. Thorac Cardiovasc. Surg. 2010; 140(6):1218-1219**
9. **Sloots KL. and Dobson GP.** *Normokalemic adenosine-lidocaine cardioplegia: importance of maintaining a polarized myocardium for optimal arrest and reanimation.* **J Thorac Cardiovasc Surg. 2010; 139(6):1576-86**
10. **Rudd DM. and Dobson GP.** *Towards a new cold and warm non-depolarising normokalemic arrest paradigm for orthotopic heart transplantation.* **J Thorac Cardiovasc Surg. 2009; 137:198-207**
11. **Jin ZX., Zhang SL., Wang XM., Bi. SH., Xin M, Zhou JJ., Cui Q, Duan WX., Wang HB., Yi DH.** *The myocardial protective effects of a moderate-potassium adenosine-lidocaine cardioplegia in pediatric cardiac surgery.*
J Thorac Cardiovasc Surg. 2008; 136(6):1450-5
12. **O'Rullian JJ., Clayson SE., Peragallo R.** *Excellent outcomes in a case of complex re-do surgery requiring prolonged cardioplegia using a new cardioprotective approach: Adenocaine®.*
J Extra Corpor Technol. 2008; 40(3):203-5
13. **Sloots KL., Vinten-Johansen J, Dobson GP.** *Warm non-depolarizing adenosine and lidocaine cardioplegia: continuous versus intermittent delivery.* **J Thorac Cardiovasc Surg. 2007; 133(5):1171-8**
14. **Canyon SJ., and Dobson GP.** *The effect of adenosine and lidocaine intravenous infusion on myocardial high-energy phosphates and pH during regional ischemia in the rat model in vivo.*
Can. J. Physiology and Pharmacology. 2006; 84(8-9):903-12
15. **Canyon SJ., and Dobson GP.** *Pretreatment with an adenosine A₁ receptor agonist and: a possible alternative to myocardial ischemic preconditioning.* **J Thorac Cardiovasc Surg. 2005; 130(2):371-7**

LIST OF PUBLICATIONS ON ADENOCAINE® COMPOUND

16. **Corvera JS., Kin H., Dobson GP., Kerendi F., Halkos ME., Katzmark S., Payne CS., Zhao ZQ., Guyton RA., Vinten-Johansen J.** *Polarized arrest with warm or cold adenosine lidocaine blood cardioplegia is equivalent to hypothermic potassium blood cardioplegia.* **J Thorac Cardiovasc Surg. 2005; 129(3):599-606**
17. **Dobson GP.** *Organ arrest, Protection and Preservation: Natural Hibernation to Cardiac Surgery.* **Comp. Biochem. Physiol. 2004; 139(3):469-85. Invited Review**
18. **Dobson GP. and Jones M.** *Adenosine and Lidocaine: A new concept in non-depolarising surgical myocardial arrest, protection and preservation.* **J Thorac Cardiovasc Surg. 2004; 127(3):794-805**
19. **Canyon SJ. and Dobson GP.** *Protection against ventricular arrhythmias and cardiac death using adenosine and lidocaine during regional ischemia in the in vivo rat.* **Am J Physiol Heart Circ Physiol. 2004; 287(3):H1286-95**
20. **Dobson GP. and Jones MW.** *Adenosine and Lignocaine: a new concept in cardiac arrest and preservation.* **Ann Thorac Surg. 2003; 75 (2) S746 (abstract)**

CONTACT INFORMATION:

For more information, please contact CAPS at **(800) 853-6498** or visit **www.capspharmacy.com/Adenocaine** or visit **www.Adenocaine.com**