Adenocor

Adenosine

Solution for Injection

[sanofi logo]

1. Trade Name of Medicinal Product
Adenocor

2. Qualitative and Quantitative Composition
Each vial contains 6 mg of adenosine per 2 ml (3 mg/ml)
For excipients, see 6.1

3. Pharmaceutical Form
Solution for injection
Clear, colourless solution

4. Clinical Particulars

4.1 Therapeutic Indications

Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome).

Diagnostic Indications

Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although Adenocor will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity.
Sensitisation of intra-cavitary electrophysiological investigations.

4.2 Posology and Method of Administration

Adenocor is intended for hospital use only with monitoring and cardiorespiratory resuscitation equipment available for immediate use. It should be administered by rapid IV bolus injection according to the ascending dosage schedule below. To be certain the solution reaches the systemic circulation administer either directly into a vein or into an IV line. If given into an IV line it should be injected as proximally as possible, and followed by a rapid saline flush.
Adenocor should only be used when facilities exist for cardiac monitoring. Patients who develop high-level AV block at a particular dose should not be given further dosage increments.

Therapeutic dose

Adult:
Initial dose: 3 mg given as a rapid intravenous bolus (over 2 seconds).
Second dose: If the first dose does not result in elimination of the supraventricular tachycardia within 1 to 2 minutes, 6 mg should be given also as a rapid intravenous bolus.
Third dose: If the second dose does not result in elimination of the supraventricular tachycardia within 1 to 2 minutes. 12mg should be given also as a rapid intravenous bolus.
Additional or higher doses are not recommended.

Paediatric Population

The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available. No controlled paediatric study has been undertaken. The level of evidence does not allow a recommended posology.

Elderly

See dosage recommendations for adults.

Diagnostic dose

The above ascending dosage schedule should be employed until sufficient diagnostic information has been obtained.
Method of administration: Rapid intravenous injection only.

4.3 Contraindications

Adenocor is contraindicated for patients presenting:

- Known hypersensitivity to adenosine or to any of the excipients
- Sick sinus syndrome, second or third degree Atrio-Ventricular (AV) block (except in patients with a functioning artificial pacemaker)
- Chronic obstructive lung disease with evidence of bronchospasm (e.g. asthma, bronchiale)
- Long QT syndrome
- Severe hypotension
- Decompensated states of heart failure

4.4 Special Warnings and Precautions for Use

Special warnings:

Due to the possibility of transient cardiac arrhythmias arising during conversion of the supraventricular tachycardia to normal sinus rhythm, administration should be carried out in a hospital setting with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary. During administration, continuous ECG monitoring is necessary as life-threatening arrhythmia might occur (see section 4.2).

Because it has the potential to cause significant hypotension, adenosine should be used with caution in patients with left main coronary stenosis, uncorrected hypovolemia, stenotic valvular heart disease, left to right shunt, pericarditis or pericardial effusion, autonomic dysfunction or stenotic carotid artery disease with cerebrovascular insufficiency.

Adenosine should be used with caution in patients with recent myocardial infarction, severe heart failure, or in patients with minor conduction defects (first degree AV block, bundle branch block) that could be transiently aggravated during infusion.

Adenosine should be used with caution in patients with atrial fibrillation or flutter and especially in those with an accessory by-pass tract since particularly the latter may develop increased conduction down the anomalous pathway.

Rare cases of severe bradycardia have been reported. Some occurred in early post heart transplant patients; in the other cases, occult sino-atrial disease was present. The occurrence of severe bradycardia should be taken as a warning of underlying disease and could potentially favour the occurrence of torsades de pointes, especially in patients with prolonged QT intervals.

In patients with recent heart transplantation (less than 1 year) an increased sensitivity of the heart to adenosine has been observed.

Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, Adenocor's efficacy should be unaffected by hepatic or renal insufficiency.

As dipyridamole is a known inhibitor of adenosine uptake, it may potentiate the action of Adenocor. It is therefore suggested that Adenocor should not be administered to patients receiving dipyridamole; if use of Adenocor is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenocor should be greatly reduced. (see section 4.5 Interactions with other Medicaments and other forms of Interaction).

Precautions:

The occurrence of angina, severe bradycardia, severe hypotension, respiratory failure (potentially fatal), or asystole/cardiac arrest (potentially fatal), should lead to immediate discontinuation of administration.

Adenosine may trigger convulsions in patients who are susceptible to convulsions. In patients with history of convulsions/seizures, the administration of adenosine should be carefully monitored.

Because of the possible risk of torsades de pointes, Adenocor should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Adenocor is contraindicated in patients with Long QT syndrome (see section 4.3).

Adenosine may precipitate or aggravate bronchospasm (see sections 4.3 and 4.8).

Adenosine contains 9 mg sodium chloride per ml (corresponding to 3.54 mg sodium per ml). To be taken into consideration by patients on a controlled sodium test.

4.5 Interactions with other Medicaments and other forms of Interaction

Dipyridamole inhibits adenosine cellular uptake and metabolism, and potentiates the action of adenosine. In one study dipyridamole was shown to produce a 4-fold increase in adenosine actions. Asystole has been reported following concomitant administration. It is therefore suggested that Adenocor should not be administered to patients receiving dipyridamole; if use of Adenocor is essential, dipyridamole should be stopped 24 hours before hand, or dose of Adenocor should be greatly reduced. (see section 4.4 Special Warnings and Precautions for Use.)

Aminophylline, theophylline and other xanthines are competitive adenosine antagonists and should be avoided 24 hours prior to use of adenosine.

Food and drinks containing xanthines (tea, coffee, chocolate and cola) should be avoided at least 12 hours prior to use of adenosine.

Adenocor may interact with drugs tending to impair cardiac conduction.

4.6 Pregnancy and Lactation

Pregnancy: There are no or limited data from the use of adenosine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Adenosine is not recommended during pregnany unless the physician considers the benefits to outweigh the potential risks.

Lactation: It is unknown whether adenosine metabolites are excreted in human milk. Adenocor should not be used during breast-feeding.

4.7 Effects on Ability to Drive and Use Machines

Not applicable.

4.8 Undesirable Effects

Adverse reactions are ranked under heading of the frequency: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000 <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000). Not known (cannot be estimated from available data).

These side effects are generally mild, of short duration (usually less than 1 minute) and well tolerated by the patient. However severe reactions can occur.

Methylxanthines, such as IV aminophylline or theophylline have been used to terminate persistent side effects (50-125 mg by slow intravenous injection).

• Nervous system disorders

Common: headache, dizziness/ lightheadedness

Uncommon: head pressure

Very rarely: transient and spontaneously and rapidly reversible worsening of intracranial hypertension

Not known: loss of consciousness/ syncope, convulsions, especially in predisposed patients (see section 4.4)

• Psychiatric disorders

Common: apprehension

• Gastro-intestinal system disorders

Common: nausea

• Cardiovascular disorders:

Very common: bradycardia, asystole, sinus pause, atrioventricular block, atrial extrasystoles, skipped beats, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia

Uncommon: sinus tachycardia, palpitations

Very rare: severe bradycardia which is not corrected by atropine and possibly requiring temporary pacing, atrial fibrillation, ventricular excitability disorders including ventricular fibrillation and torsade de pointes (see section 4.4)
Not known: asystole/ cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease/ cardiac disorder (see section 4.4), MI/ ST segment elevation especially in patients with pre-existing severe CAD (see section 4.4)

• Eye disorders

Uncommon: blurred vision

• Gastrointestinal disorders

Common: nausea
Uncommon: metallic taste
Not known: vomiting

• Respiratory, thoracic and mediastinal disorders:

Very common: dyspnea (or the urge to take a deep breath)
Uncommon: hyperventilation
Very rare: bronchospasm (see section 4.4), apnoea/ respiratory arrest
Cases of respiratory failure, bronchospasm, apnea, and respiratory arrest with fatal outcome have been reported.

• Vascular disorders

Very common: flushing
Not Known: hypotension sometimes severe, Cerebrovascular accident/transient ischemic attack;, secondary to the hemodynamic effects of adenosine including hypotension (see Warnings and Precautions)

• Immune system disorders

Not known: Anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash)

• General disorders and administration site conditions

Very common: chest pressure/ pain feeling of thoracic constriction/ oppression
Common: burning sensation
Uncommon: sweating, feeling of general discomfort/ weakness/ pain
Very rarely: injection site reactions

4.9 Overdose

Overdosage would cause severe hypotension, bradycardia or asytole. The half-life of adenosine in blood is very short, and side effects (when they occur) would quickly resolve. Administration of IV aminophylline or theophylline may be needed. Pharmacokinetic evaluation indicates that methyl xanthines are competitive antagonists to adenosine, and that therapeutic concentrations of theophylline block its exogenous effects.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

ATC Code: Other Cardiac Preparations C01EB10
Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect
Antiarrhythmic drug
Adenosine is a purine nucleoside which is present in all cells of the body. Animal pharmacology studies have in several species shown that Adenosine has a negative dromotropic effect on the atrioventricular (AV) node.
In man Adenocor (Adenosine) administered by rapid intravenous injection slows conduction through the AV node. This action can interrupt re-entry circuits involving the AV node and restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias. Once the circuit has been interrupted, the tachycardia stops and normal sinus rhythm is re-established.
One acute interruption of the circuit is usually sufficient to arrest the tachycardia.
Since atrial fibrillation and atrial flutter do not involve the AV node as part of a re-entry circuit, Adenosine will not terminate these arrhythmias.
By transiently slowing AV conduction, atrial activity is easier to evaluate from ECG recordings and therefore the use of Adenosine can aid the diagnosis of broad or narrow complex tachycardias.
Adenosine may be useful during electrophysiological studies to determine the site of AV block or to determine in some cases of pre-excitation, whether conduction is occurring by an accessory pathway or via the AV node.

5.2 Pharmacokinetic Properties

Adenosine is impossible to study via classical ADME protocols. It is present in various forms in all cells of the body where it plays an important role in energy production and utilisation systems. An efficient salvage and recycling system exists in the body, primarily in the erythrocytes and blood vessel endothelial cells. The half-life in vitro is estimated to be <10 seconds. The in vivo half-life may be even shorter.

5.3 Pre-clinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Chloride, Water for Injections

6.2 Incompatibilities

Compatibility with other medicines is not known.

6.3 Shelf-Life

36 months. Any portion of the vial not used at once should be discarded.

6.4 Special Precautions for Storage

Store below 30°C. Do not refrigerate.

6.5 Nature and Contents of Container

Clear, type I glass vials with chlorobutyl rubber closures secured with aluminium caps. Packs of 6 vials in plastic trays in cardboard cartons.

6.6 Instructions for Use/ Handling

None.

7. Marketing Authorisation Holder

7.1 Product Registrant (Singapore)

Sanofi-Aventis Singapore Pte Ltd
38 Beach Road
#18-11 South Beach Tower Singapore 189767

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