Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adenocor 3 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 6mg of adenosine per 2ml (3mg/ml).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
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.

Paediatric population
Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia in children aged 0 to 18 years.

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: 3mg given as a rapid intravenous bolus (injection over 2 seconds).

Second dose: If the first dose does not result in elimination of the supraventricular tachycardia within 1 to 2 minutes, 6mg 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.

Elderly
See dosage recommendations for adults.

Diagnostic dose

The above ascending dosage schedule should be employed until sufficient diagnostic information has been obtained.

Paediatric population

During administration of adenosine cardio-respiratory resuscitation equipment must be available for immediate use if necessary.
Adenosine is intended for use with continuous monitoring and ECG recording during administration.

The dosing recommended for the treatment of paroxysmal supraventricular tachycardia in the paediatric population is:
-first bolus of 0.1 mg/kg body weight (maximum dose of 6mg)
-increments of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia (maximum dose of 12mg).

Method of administration
Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an IV line. If given into an IV line it should be injected through as proximally as possible, and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used.

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 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:
Adenosine is intended for use 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. (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 or severe heart failure. Adenosine should be used with caution in patients with minor conduction defects (first degree A-V 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-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. Severe bradycardia wouldfavour the occurrence of torsades de pointes, especially in patients with prolonged QT intervals.

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

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

Adenosine may precipitate or aggravate bronchospasm. See sections 4.3 and 4.8

Precautions:
Adenosine is intended for use by physicians familiar with the product (see Section 4.2 Posology and Method of Administration) in a hospital setting with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary.

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.

This medicine contains less than 1 mmol sodium (23mg) per 2ml, that is to say essentially "sodium free"

Paediatric population
Adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome. Also see section 5.1.

The efficacy of intraosseus administration has not been established.

4.5 Interaction with other medicinal products and other forms of interactions

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 activity.
It is therefore suggested that adenosine should not be administered to patients receiving dipyrimadole;if use of adenosine is essential, dipyridamole should be stopped 24 hours beforehand, or the dose of adenosine should be greatly reduced.

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

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

Adenosine may interact with drugs tending to impair cardiac conduction.

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

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).

Frequencies provided refer to legacy data. For newly included safety items, which are based exclusively on post-marketing experience, the frequency listed is: "Not known". The following CIOMS frequency rating is used, where applicable:
Very common: (>1/10); Common : (>1/100,<1/10); Uncommon: (>1/1000,<1/100), Rare: (>1/10000, < 1/10000, Very rare: (<1/10000), Not known (cannot be estimated from available data.).

· **Nervous system disorders**
Common:
- headache,
- dizziness / lightheadedness
Uncommon:
- head pressure
Very rare:
- transient, and spontaneously rapidly reversible worsening of intracranial hypertension
Not known:
- loss of consciousness/syncope
- convulsions, especially in predisposed patients (see Section 4.4 Special Warnings and Precautions for Use)

· **Psychiatric disorders**
Common:
-apprehension

· **Eye disorders**
Uncommon:
-blurred vision

· **Vascular disorders**
Very common:
-flushing
Not known:
-hypotension sometimes severe
-cerebrovascular accident/transient ischemic attack,(See section 4.4 Special Warnings and Precautions for Use)

· **Gastro-intestinal disorders**
Common:
-nausea
Uncommon:
-metallic taste
Not known:
-vomiting

· **Cardiac disorders:**
Very common:
- bradycardia
- sinus pause, skipped beats
- atrial extrasystoles
- atrio-ventricular block
- ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia
Uncommon:
- sinus tachycardia
- palpitations
Very rare:
- atrial fibrillation

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

· **Respiratory, thoracic and mediastinal disorders:**
Very common:
- dyspnoea (or the urge to take a deep breath)
Uncommon:
-hyperventilation
Very rare:
- bronchospasm (see Section 4.4 Special Warnings and Precautions for Use)
Not known:
- respiratory failure (see Section 4.4 Special Warnings and Precautions for Use)
- apnoea/respiratory arrest.
Cases with fatal outcome, of respiratory failure, of bronchospasm, and of apnoea/respiratory arrest have been reported.

· **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 rare:
- injection site reactions

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage would cause severe hypotension, bradycardia or asystole. 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. Treatment of any prolonged adverse effects should be individualised and directed towards the specific symptom.

Methylxanthines, such as caffeine, theophylline, and aminophylline are competitive antagonists of adenosine. Intravenous aminophylline or theophylline may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antiarrhythmic drug.

Adenosine is a purine nucleoside which is present in all cells of the body. Animal pharmacology studies in several species have 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.

A single 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 Adenocor can aid the diagnosis of broad or narrow complex tachycardias.

Adenocor 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.

Paediatric population

No controlled studies have been conducted in paediatric patients with adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, the safety and efficacy of adenosine in children aged 0 to 18 years with PSVT is considered established based on extensive clinical use and literature data (open label studies, case reports, clinical guidelines).

Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years.

Studies were heterogenic in terms of age, and dosing schedules. SVT was terminated in 72 to 100% of cases in most of the published studies. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. Several studies discussed a lack of response to starting doses less than 100mcg/kg.

Depending on the child's clinical history, symptoms and ECG diagnosis, adenosine has been used in clinical practice under expert supervision in children with stable wide-QRS complex tachycardia and Wolff-Parkinson-White syndrome however the currently available data does not support a paediatric indication. In total 6 cases of adenosine-induced arrhythmias (3 atrial fibrillation, 2 atrial flutter, 1 ventricular fibrillation) have been described in 6 children aged 0 to 16 years with manifest or concealed WPW syndrome, of which 3 spontaneously recovered and 3 needed amiodarone +/- cardioversion (see also section 4.4).

Adenosine has been used as an aid to diagnosis of broad or narrow complex supraventricular tachycardias in same doses as for treatment of supraventricular tachycardia. Although adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity. However, the currently available data does not support a paediatric indication for the use of adenosine for diagnostic purposes.

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 *in vitro* half life is estimated to be <10 seconds. The *in vivo* half life may be even shorter.

5.3 Preclinical 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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
Any portion of the vial not used at once should be discarded.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate.

6.5 Nature and contents of container

Packs of six clear, Type I glass vials with chlorobutyl rubber closures secured with aluminium caps containing 2 ml of solution.

6.6 Special precautions for disposal and other handling

Do not use if any particles or discolouration are noticed in the solution.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

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