SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adenosine 6 mg/2 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 3 mg adenosine.

Each ampoule contains 6 mg of adenosine per 2 ml (3 mg/ml6 mg/2 ml).

Excipient(s) with known effect:

Each ampoule contains 7.08 mg of sodium per ampoule (as sodium chloride).

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 diet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless, sterile solution, practically free from particles.

Solution as a pH between 4.5 – 7.5 and an Osmolality of 270 - 330 mOsm/Kg.

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).

Paediatric population

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

Diagnostic indications

Aid to diagnosis of broad or narrow complex supraventricular tachycardias.

Although Adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of atrioventricular (AV) conduction helps diagnosis of atrial activity.

Sensitisation of intra-cavitary electrophysiological investigations.

4.2 Posology and method of administration

Adenosine is intended for hospital use only with monitoring and cardiorespiratory resuscitation equipment available for immediate use.

Adenosine 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.

Posology

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. 12 mg should be given also as a rapid intravenous bolus.

Additional or higher doses are not recommended.

Paediatric population

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 6 mg)
- increments of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia (maximum dose of 12 mg).

Elderly

See dosage recommendations for adults.

Method of administration

It should be administered by rapid IV bolus injection according to the ascending dosage schedule above. 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. If administered through a peripheral vein, a large bore cannula should be used.

Adenosine 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.

Diagnostic dose

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

4.3 Contraindications

Adenosine is contraindicated for patients presenting:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 A-V block, bundle branch block) that could be transiently aggravated during injection.

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, adenosine'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 adenosine. It is therefore suggested that adenosine should not be administered to patients receiving dipyridamole; if use of adenosine is essential, dipyridamole should be stopped 24 hours before hand, or the dose of adenosine should be greatly reduced (see section 4.5).

Adenosine has been shown to be ineffective in patients with atrial or ventricular tachycardia or with tachycardia attributable to atrial fibrillation or atrial flutter.

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 should also be used with caution if there is a history of unstable angina pectoris.

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, adenosine should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Adenosine 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), i.e. 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 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 adenosine should not be administered to patients receiving dipyridamole; if use of adenosine is essential, dipyridamole should be stopped 24 hours before hand, or the dose of adenosine should be greatly reduced (see section 4.4).

Aminophylline, theophylline and other xanthines, as caffeine, 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 other medicinal products which inhibit conduction (e.g. beta blockers, digitalis, verapamil) or accelerate conduction (e.g. beta-sympathomimetics).

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.

Breastfeeding

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).

Adverse events are ranked under the heading of the frequency:

Very common (>1/10), Common (>1/100, <1/10), Uncommon (>1/1000, <1/100), Rare (>1/10000, <1/1000), Very rare (<1/10000), Not known (cannot be estimated from available data).

Immune system disorders	
Not known	Anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash)
Psychiatric disorders	
Common	Apprehension
Nervous System disorders	
Common	Headache,
	Dizziness, light-headedness
Uncommon	Increased intracranial 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)
Eye disorders	
Uncommon	Blurred vision
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
	Asystole (usually transient and self-limiting

Uncommon	Sinus tachycardia
	Palpitations
Very rare	Atrial fibrillation
	Severe bradycardia not corrected by atropine and possibly requiring temporary pacing
	Ventricular excitability disorders, including ventricular fibrillation and torsade de pointes (see section 4.4)
Not known	Hypotension sometimes severe
	Asystole / cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease / cardiac disorder
	Myocardial infarction/elevation of ST segment, especially in patients with coronary artery disease - pre-existing severe coronary artery disease (see section 4.4)
	Arteriospasm coronary which may lead to myocardial infarction
Vascular disorders	
Very common	Flushing
Not known	Stroke / transient ischemic attack; secondary to the hemodynamic effects of adenosine, including hypotension (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)
Not known	Respiratory failure (see section 4.4)
	Apnoea / Respiratory arrest,
	Cases of respiratory failure, bronchospasm, apnoea, and respiratory arrest with fatal outcome have been reported.
Gastrointestinal disorders	
Common	Nausea
Uncommon	Metallic taste
Not known	Vomiting
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 theYellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. 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

Pharmacotherapeutic group: Other Cardiac Preparations, ATC code: C01EB10

Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect

Antiarrhythmic drug.

Mechanism of action

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 adenosine when 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.

Pharmacodynamic effects

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.

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 pharmacokinetic 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 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

The ampoule content is intended for single dose administration. Any remaining portion of the ampoule content should be discarded immediately after initial use.

6.4 Special precautions for storage

Do not store above 30°C.

Do not refrigerate.

6.5 Nature and contents of container

Clear, type I glass ampoules.

Packs of 10 ampoules in plastic trays in cardboard cartons.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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