SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adenosine 3 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 3 mg adenosine.

Each 2 ml vial contains 6 mg adenosine.

Excipient with known effect:

Each ml of solution contains 3.542 mg of sodium

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear and colourless to almost colourless solution, free from visible particle.

Osmolarity: Between 250 mOsmol/L to 360 mOsmol/L.

pH: Between 4.50 and 7.50

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 aged 0 to 18 years.

Diagnostic Indications

Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although Adenosine 3 mg/ml solution for injection 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

Adenosine 3 mg/ml solution for injection is intended for hospital use only with monitoring and cardiorespiratory resuscitation equipment available for immediate use.

Method of administration

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.

Adenosine 3 mg/ml solution for injection 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:	3mg 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, 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.

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.

Each vial is intended for single use. The solution should be examined visually for particulate matter and discoloration prior to administration. Only clear and colourless solution should be used.

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

Adenosine 3 mg/ml solution for injection is contraindicated for patients presenting:

- known hypersensitivity to the adenosine 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. (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 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, Adenosine 3 mg/ml solution for injection'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 3 mg/ml solution for injection. It is therefore suggested that Adenosine 3 mg/ml solution for injection should not be administered to patients receiving dipyridamole; if use of Adenosine 3 mg/ml solution for injection is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenosine 3 mg/ml solution for injection 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, Adenosine 3 mg/ml solution for injection should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Adenosine 3 mg/ml solution for injection 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 diet.

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 3 mg/ml solution for injection should not be administered to patients receiving dipyridamole; if use of Adenosine 3 mg/ml solution for injection is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenosine 3 mg/ml solution for injection 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 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 3 mg/ml solution for injection may interact with drugs tending to impair cardiac conduction.

4.6 Fertility, Pregnancy and lactation

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 3 mg/ml solution for injection should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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). 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).

Frequency	**Side effects**
Psychiatric disorders	
Common	- Apprehension
Nervous system disorders	
Common	- Headache - Dizziness, light-headedness
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)
Eye disorders	
Uncommon	- Blurred vision
Immune system disorders:	
Not known:	- anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash).
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 - 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 (see section 4.4) - Arteriospasm coronary which may lead to myocardial infarction.
Vascular disorders	
Very common	- Flushing
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)
Not known	Respiratory failure (see section 4.4) - Apnea / Respiratory arrest,
Cases of Respiratory failure, bronchospasm, apnea, 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 is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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: C01EB 10

Endogenous nucleoside with peripheral vasodilator / antiarrhythmic effect

Mechanism of Action:

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 Adenosine 3 mg/ml solution for injection (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.

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 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

Water for Injections

Sodium Chloride

6.2 Incompatibilities

Compatibility with other medicines is not known.

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

6.3 Shelf life

Unopened: 24 Months

The product should be used immediately after opening.

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

6.4 Special precautions for storage

Do not store above 25 °C. Do not refrigerate.

6.5 Nature and contents of container

Sulfur treated clear tubular Glass vial, Ph. Eur. Type-I with Teflon coated rubber closure and 2 ml fill volume.

Packs of 5, 6, 10 and 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused solution and the containers should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford, Norfolk IP24 3SE, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00116/0685

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/03/2019

10 DATE OF REVISION OF THE TEXT

28/08/2023