Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adenosine 30mg/10ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 30mg of adenosine per 10ml (3mg/ml).
Excipient: each vial contains approximately 36 mg of sodium per vial (10ml).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Intravenous (IV) adenosine infusion is a coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate.

4.2 Posology and method of administration

Adenosine infusion is intended for use in hospitals with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary.
It should be administered following the same procedure as for exercise testing where facilities for cardiac monitoring and cardio-respiratory resuscitation are available. During administration of adenosine infusion continuous ECG control is necessary as life-threatening arrhythmia might occur. Heart rate and blood pressure should be monitored every minute.

Posology:

Adults:

1. Adenosine infusion should be administered undiluted as a continuous peripheral intravenous infusion at a dose of 140 µg/kg/min for six minutes using an infusion pump. Separate venous sites for adenosine infusion and radionuclide administration are recommended to avoid an adenosine bolus effect.

2. After three minutes of adenosine infusion, the radionuclide is injected to ensure sufficient time for peak coronary blood flow to occur. The optimal vasodilator protocol is achieved with six minutes of adenosine infusion.

3. To avoid an adenosine bolus effect, blood pressure should be measured in the arm opposite to the adenosine infusion.

The table below is given as a guide for adjustment of the infusion rate of undiluted adenosine infusion, in line with bodyweight (total dose 0.84 mg/kg).

Patient Weight (kg)	Infusion Rate (ml/min)
45-49	2.1
50-54	2.3
55-59	2.6
60-64	2.8
65-69	3.0
70-74	3.3

75-79	3.5
80-84	3.8
85-89	4.0
90-94	4.2
95-99	4.4
100-104	4.7

Paediatric population

The safety and efficacy of adenosine in children aged 0 to 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Elderly:

See dosage recommendations for adults.

4.3 Contraindications

Adenosine infusion is contraindicated in patients suffering from:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second or third degree atrioventricular (AV) block, sick sinus syndrome, except in patients with a functioning artificial pacemaker.
- Long QT syndrome.
- Severe hypotension.
- Unstable angina not successfully stabilised with medical therapy.
- Decompensated states of heart failure.
- Chronic obstructive lung disease with evidence of bronchospasm (e.g. asthma bronchiale).
- Concomitant use of dipyridamole (see section 4.5)

4.4 Special warnings and precautions for use

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 infusion 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 infusion should be discontinued in any patient who develops persistent or symptomatic hypotension. There have been reports of cerebrovascular accident/transient ischemic attack, secondary to the haemodynamic effects of adenosine.

There have been reports of myocardial infarction shortly after use of Adenosine Infusion. Adenosine Infusion should be used with caution in patients with recent myocardial infarction, 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 may trigger convulsions in patients who are susceptible to convulsions.

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 and should lead to treatment discontinuation. Severe bradycardia would favour the occurrence of torsades de pointes, especially in patients with prolonged QT intervals. But to date, no case of torsades de pointes has been reported when adenosine is continuously infused.

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).

Adenosine infusion contains approximately 36mg sodium per vial (10ml). To be taken into consideration by patients on a controlled sodium diet.

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 actions. It is therefore suggested that adenosine infusion should not be administered to patients receiving dipyridamole; if use of adenosine infusion is essential, dipyridamole should be stopped 24 hours before hand, 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 Infusion.

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

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.

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Effects related to the known pharmacology of adenosine are frequent, but usually self-limiting and of short duration. Discontinuation of infusion may be necessary if the effect is intolerable.

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 (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), 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).

Cardiac Disorders:
•common: ST segment depression, sustained or non-sustained ventricular tachycardia, AV block (see section 4.4).

If sustained second or third degree AV block develops the infusion should be discontinued. If first degree AV block occurs, the patient should be observed carefully as a quarter of patients will progress to a higher degree of block.
- uncommon: bradycardia sometimes severe (see section 4.4)
- not known: asystole/cardiac arrest (sometimes fatal, especially in patients with underlying ischemic heart disease/cardiac disorders, see section 4.4): sinus tachycardia, atrial fibrillation, ventricular fibrillation.

Nervous system disorders
- very common: headache
- common: dizziness, light-headedness, paraesthesia
- rare: tremor, drowsiness
- not known: loss of consciousness / syncope, convulsions, especially in predisposed patients (see section 4.4)

Eye disorders
- rare: blurred vision

Ear and labyrinth disorders:
- rare: tinnitus

Respiratory, thoracic and mediastinal disorders:
- very common: dyspnea (or the urge to breathe deeply)
- rare: bronchospasm (see section 4.4), nasal congestion
- very rare: respiratory failure (see section 4.4)
- not known: apnea/respiratory arrest

Cases with fatal outcome of respiratory failure, of bronchospasm, and of apnea/respiratory arrest have been reported.

Gastro-intestinal disorders:
- very common: abdominal discomfort
- common: dry mouth
- uncommon: metallic taste
- not known: nausea, vomiting.

Renal and Urinary disorders:
- rare: urinary urgency

Vascular disorders:
- very common: flushing
- Common: hypotension, sometimes severe (see section 4.4)

General disorders and administration site conditions:
- very common: chest pain or pressure, feeling of thoracic constriction/oppression
- common: throat, neck and jaw discomfort
- uncommon: sweating, discomfort in the leg, arm or back, feeling of general discomfort weakness/pain
- very rare: injection site reactions

Reproductive system and breast disorders:
- rare: nipple discomfort

Psychiatric disorders:
- uncommon: nervousness

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: http://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 of adenosine infusion (when they occur) would quickly resolve when the infusion is discontinued. Administration of IV aminophylline or theophylline may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Cardiac Preparations,
ATC code: C01EB 10

Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine exerts its pharmacological effects through activation of purine receptors (cell-surface A1 and A2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A2 receptors in smooth muscle cells. Adenosine may reduce vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Intracoronary Doppler flow catheter studies have demonstrated that intravenous adenosine at 140 µg/kg/min produces maximum coronary hyperaemia (relative to intracoronary papaverine) in approximately 90% of cases within 2-3 minutes of the onset of the infusion. Coronary blood flow velocity returns to basal levels within 1-2 minutes of discontinuing the adenosine infusion.

The increase in blood flow caused by adenosine in normal coronary arteries is significantly more than that in stenotic arteries. Adenosine redirects coronary blood flow from the endocardium to the epicardium and may reduce collateral coronary blood flow thereby inducing regional ischaemia.

Continuous infusion of adenosine in man has been shown to produce a mild dose-dependent fall in mean arterial pressure and a dose-related positive chronotropic effect, most likely caused by sympathetic stimulation. The onset of this reflex increase in heart rate occurs later than the negative chronotropic/dromotropic effect. This differential effect is mostly observed after bolus injection thus explaining the potential use of adenosine as a treatment for supraventricular arrhythmias when administered as a bolus or as a coronary vasodilator when administered as an infusion.

Although Adenosine Infusion affects cardiac conduction, it has been safely and effectively administered in the presence of other cardioactive or vasoactive drugs such as beta adrenergic blocking agents, calcium channel antagonists, nitrates, ACE inhibitors, diuretics, digitalis or anti-arrhythmics.

Paediatric population
Literature review identified three studies where intravenous adenosine infusion was used in conjunction with radionuclide myocardial perfusion
imaging at a dose of 0.14 mg/kg body weight/min for 2-4 minutes in paediatric patients aged 1 month to 18 years. The largest study included 47 patients aged 1 month to 18 years of age and reported 87% sensitivity (CI 52-97%) and 95% specificity (CI 79-99%) for cardiovascular magnetic resonance imaging under pharmacological stress with intravenous adenosine in a dose of 0.14 mg/kg/min for 3 minutes. No adverse events were reported in the study.
However, the currently available data is considered very limited to support the use of adenosine for diagnostic purposes in the paediatric population.

5.2 Pharmacokinetic properties

It is impossible to study adenosine in classical pharmacokinetic studies. It is present in various forms in all the 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 erythrocytes and blood vessel endothelial cells. The half-life in vitro is estimated to be less than 10 seconds. The in vivo half-life may be even shorter.

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

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to those already included in other sections of the SmPC.
No controlled reproductive studies were conducted in animals with adenosine.

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

Unopened: 36 months.

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not refrigerate. Store below 25°C.

6.5 Nature and contents of container

Clear, neutral type I glass vials (10ml) sealed with chlorobutyl rubber closures. Packs of 6 vials packed in a PVC tray in a cardboard carton.

6.6 Special precautions for disposal and other handling

Do not use if any particles or discolouration are noticed in the solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/035/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th October 2013
Date of last renewal: 30th April 2016

10 DATE OF REVISION OF THE TEXT

March 2019
CRN008T5V