SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adenoscan® 30 mg/10 ml, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial of Adenoscan® contains 30 mg of adenosine (3 mg/ml)

Excipient with known effect:
Each vial contains 1.54 mmol of sodium, which is 35.4 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Adenoscan® is a sterile clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous (IV) Adenoscan® 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

Adenoscan® 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 Adenoscan® continuous ECG control is necessary as life-threatening arrhythmia might occur. Heart rate and blood pressure should be monitored every minute.

Posology

Adults

1. Adenoscan® 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 Adenoscan® and radionuclide administration are recommended to avoid an adenosine bolus effect.
2. After three minutes of Adenoscan® 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 Adenoscan® infusion.
3. To avoid an adenosine bolus effect, blood pressure should be measured in the arm opposite to the Adenoscan® infusion.

The table below is given as a guide for adjustment of the infusion rate of undiluted Adenoscan®, 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 – 18 years old 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

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

Adenosine may trigger convulsions in patients who are susceptible to convulsions.

Adenoscan® 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).

Adenoscan® contains 35.4 mg sodium per vial (3.54 mg sodium per ml), equivalent to 1.77% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Dipyridamole inhibits adenosine cellular uptake and metabolism, and potentiates the action of Adenoscan®. In one study dipyridamole was shown to produce a 4-fold increase in adenosine actions. It is therefore suggested that Adenoscan® should not be administered to patients receiving dipyridamole; if

use of Adenoscan® is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenoscan® should be greatly reduced.

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

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

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. Adenoscan 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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <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).

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. Arteriospasm coronary which may lead to myocardial infarction.

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

Gastrointestinal 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 authorization 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 the MHRA Yellow Card Scheme at: 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 of Adenoscan® (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

Mechanism of action

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 A_1 and A_2 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 A_2 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.

Pharmacodynamic effects

Intracoronary Doppler flow catheter studies have demonstrated that intravenous Adenoscan® 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 Adenoscan® infusion.

The increase in blood flow caused by Adenoscan® in normal coronary arteries is significantly more than that in stenotic arteries. Adenoscan® 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 Adenoscan® 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

Distribution

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.

Elimination

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 Adenoscan® should be unaffected by hepatic or renal insufficiency.

5.3 Preclinical safety data

Because adenosine is naturally present in all living cells, studies in animals to evaluate the carcinogenic potential of Adenoscan® (adenosine) have not been performed.
No controlled reproductive studies were conducted in animals with adenosine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

The shelf life of the unopened product is 3 years.
The medicinal product should be used immediately after opening

6.4 Special precautions for storage

Do not refrigerate.
See section 6.3

6.5 Nature and contents of container

Type I glass vials with chlorobutyl rubber stoppers, packs with 6 vials

6.6 Special precautions for disposal and handling

See section 4.2

The product is for single use only.

The product should be inspected visually for particulate matter and colouration prior to administration. Where the visual appearance of the product may have changed, the vial should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT

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