Public Assessment Report

Decentralised Procedure

ADENOSINE 30MG/10ML SOLUTION FOR INFUSION

Procedure No: UK/H/4126/002/DC

UK Licence No: PL 29831/0456

WOCKHARDT UK LTD
LAY SUMMARY

On 03 August 2011, Germany, Poland and the UK agreed to grant a Marketing Authorisation to Wockhardt UK Ltd for the medicinal product Adenosine 30mg/10ml Solution for Infusion (PL 29831/0456; UK/H/4126/002/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 01 September 2011.

This product is a prescription-only medicine (POM) for diagnostic use only. It is given before a test called “myocardial perfusion imaging” to look at your heart. This works by opening up your heart's blood vessels and allowing blood to flow more freely. This allows the radiopharmaceutical medicine to get into your heart and permits the doctor to assess your heart condition. This is used if you are unable to exercise or if an exercise stress test is not possible.

Adenosine 30mg/10ml Solution for Infusion contains the active ingredient adenosine which belongs to a group of medicines called coronary vasodilators.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Adenosine 30mg/10ml Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.
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Module 1

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<td>MA Holder</td>
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Module 2

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.

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).

<table>
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<th>Patient Weight (kg)</th>
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<td>100-104</td>
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</table>
Paediatric population
The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available.

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.

- 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.

Adenosine 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 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. 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 such as caffeine 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.

Lactation:
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).

Cardiac Disorders:
common: hypotension, sometimes severe (see section 4.4), 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

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

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 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.

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: 24 months.

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not refrigerate.

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

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 Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0456

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/09/2011

10 DATE OF REVISION OF THE TEXT
01/09/2011
Module 3

1. WHAT ADENOSINE INFUSION IS AND WHAT IT IS USED FOR

The name of your medicine is Adenosine. The active ingredient in your medicine is Adenosine. Adenosine belongs to a group of medicines called coronary vasodilators. This medicine is for diagnostic use only.

Adenosine Infusion is given before a test called myocardial perfusion imaging to look at your heart. During this test you are given a medicine called a "radionuclide agent". Adenosine Infusion works by opening up your heart's blood vessels and allowing blood to flow more freely. This allows the radionuclide agent to get into your heart. The doctor can then assess your heart condition. This is used if you are not capable of exercising or if an exercise stress test is not possible.

2. BEFORE YOU ARE GIVEN ADENOSINE INFUSION

You should not be given Adenosine Infusion if you have any of the conditions below:
- Allergic reactions (hypersensitivity) to Adenosine or any of the other ingredients in this medicine (see section 4).
- You have any active heart rhythm, for example your heart is very fast or irregular, or you have a condition where your heart has abnormal electrical activity ("accessory conduction pathway")
- You have had a heart attack or if you have had a heart transplant in the last year.
- You have any minor problem with your heart (first degree atrioventricular block or an atrial flutter block). These conditions may be temporarily aggravated when you are given Adenosine.
- You have had heart failure. Heart failure means that your heart cannot pump blood to your body. It can cause you to become short of breath.
- You have had an injection or had a blood transfusion.
- You are taking other medicines (see section 4).

3. INFORMATION FOR HEALTHCARE PROFESSIONALS

Adenosine 30mg/10ml Solution for Infusion

Please refer to the Summary of Product Characteristics (SmPC) for further details on this product.

Qualitative and Quantitative Composition

Each vial contains: 30mg of adenosine per 10ml (3%)

Preparation for injection

Suitable for injection.

4. ADVICE FOR PATIENTS

Take special care with Adenosine Infusion if you have any of the conditions below:
- Low blood volume (hypovolaemia) which is not corrected by medicines,
- Narrowing of your main artery supplying blood to your heart (heart main coronary artery),
- Narrowing of the main arteries in the neck, so not enough blood is getting to the brain,
- A heart disease which is caused by the narrowing of your heart valves (stenosis of aortic or mitral valve),
- A left ventricle in your heart, which means blood goes directly from the left side of your heart to the right side problems with a part of your nervous system called the autonomic nervous system,
- Information about the area surrounding your heart (pericardial effusion) or a build up of the fluid around your heart (pericardial effusion),
- A build up of heart failure.
- You have a heart attack or if you have had a heart transplant in the last year.
- You have any minor problem with your heart (first degree atrioventricular block or an atrial flutter block). These conditions may be temporarily aggravated when you are given Adenosine.
- You have had heart failure. Heart failure means that your heart cannot pump blood to your body. It can cause you to become short of breath.
- You have had an injection or had a blood transfusion.
- You are taking other medicines (see section 4).

5. SIDE EFFECTS

Take special care with Adenosine Infusion if you have any of the conditions below:
- Low blood volume (hypovolaemia) which is not corrected by medicines,
- Narrowing of your main artery supplying blood to your heart (heart main coronary artery),
- Narrowing of the main arteries in the neck, so not enough blood is getting to the brain,
- A heart disease which is caused by the narrowing of your heart valves (stenosis of aortic or mitral valve),
- A left ventricle in your heart, which means blood goes directly from the left side of your heart to the right side problems with a part of your nervous system called the autonomic nervous system,
- Information about the area surrounding your heart (pericardial effusion) or a build up of the fluid around your heart (pericardial effusion),
- A build up of heart failure.
- You have a heart attack or if you have had a heart transplant in the last year.
- You have any minor problem with your heart (first degree atrioventricular block or an atrial flutter block). These conditions may be temporarily aggravated when you are given Adenosine.
- You have had heart failure. Heart failure means that your heart cannot pump blood to your body. It can cause you to become short of breath.
- You have had an injection or had a blood transfusion.
- You are taking other medicines (see section 4).

6. ADDITIONAL INFORMATION

Informed consent (voluntary consent) for the administration of Adenosine Infusion is a necessary condition for use in conjunction with the administration of other medicines in patients who cannot cooperate adequately or whose cooperation is inappropriate.

Precautions and method of administration

Adenosine Infusion is preferred in cases where the patient is cooperative, and other methods of administration are not available. In patients who are unable to cooperate adequately or whose cooperation is inappropriate.

7. ADMINISTRATION

Adenosine Infusion is preferred in cases where the patient is cooperative, and other methods of administration are not available. In patients who are unable to cooperate adequately or whose cooperation is inappropriate.

8. STORAGE

Store below 25°C.

9. DISPOSAL

Do not use after the expiry date.

10. ADDITIONAL INFORMATION

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Precautions and method of administration

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12. ADDITIONAL INFORMATION

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Precautions and method of administration

Adenosine Infusion is preferred in cases where the patient is cooperative, and other methods of administration are not available. In patients who are unable to cooperate adequately or whose cooperation is inappropriate.
PAR Adenosine 30mg/10ml Solution for Infusion

UK/H/4126/002/DC

8. HOW YOU WILL BE GIVEN ADENOSINE INFUSION
Adenosine Infusion is a medicine for use in hospitals. Adenosine Infusion will be given to you by a doctor or nurse as an injection. The injection will be into one of your veins. It will be given over a period of time. Your heart rate and blood pressure will be closely monitored.

Adults
The dose you will be given will depend on your weight.
The usual dose is 140 micrograms per kilogram of body weight.
This is given over a period of six minutes through an infusion pump (a slow injection into a vein).

Children
Adenosine Infusion is not recommended for use in children.
If you have more Adenosine Infusion than you should have given to you by your doctor or nurse, it is unlikely that you will be given too much. Your doctor will carefully work out how much Adenosine Infusion you should be given.
If you have more than this medicine than you should, the following effects may happen:
- Very low blood pressure (severe hypotension)
- Slow heart rate (bradycardia)
- A heart problem (asystole)
Your doctor will be monitoring your heart throughout the procedure.

The length of time Adenosine stays in the blood is very short.
Any side effects of too much Adenosine would quickly stop when the infusion is stopped. You may be given an injection of a medicine called theophylline to help with any side effects.
If you have any further questions on the use of this product, ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Adenosine Infusion can cause side effects, although not everybody gets them.
The following side effects may be experienced when taking Adenosine Infusion. If any of the side effects get worse, tell your doctor or nurse immediately and they will decide if you should continue the infusion or not.
The side effects normally settle within seconds or minutes after the infusion is finished but you should tell your doctor or nurse if any of them happen.

Very common (affects more than 1 in 10):
- redness of the skin with a feeling of heat (flushing)
- shortness of breath or the urge to breathe deeply (dyspnoea)
- headache
- change of colour or pressure on the chest
- abdominal discomfort.

Common (affects less than 1 in 10):
- feeling dizzy, or light-headed
- unusual skin sensations such as numbness, tingling, prickling, burning or tingling on the skin (paresthesia)
- low blood pressure
- a heart problem called an atrioventricular block
- fast or irregular heartbeat (disorders of cardiac rhythm)
- dry mouth
- discomfort in throat, jaw or neck.

Uncommon (affects less than 1 in 100):
- metallic taste in your mouth
- sweating
- discomfort in leg, arm or back
- feeling of weakness or pins or needles sensation on the skin (paresthesia)
- feeling nervous
- slow heartbeat (bradycardia).

Rare (affects less than 1 in 1,000):
- difficult in breathing (bronchospasm)
- blood clots
- feeling dizzy
- blurred vision
- ringing in the ears (tinnitus)
- feeling a sudden need to urinate
- rapid disorient
- tremors.
Very rare side effects (affect less than 1 in 10,000):
- severe breathlessness or problems in breathing
- redness, pain or swelling at the site of injection.
Other side effects (frequency cannot be estimated from the available data):
- severe heart problems which can be fatal (cardiomyopathy or arrhythmia)
- breathlessness
- stopping breathing (respiratory arrest)
- feeling sick (nausea) or being sick (vomiting).
- If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE ADENOSINE INFUSION
Keep out of the reach and sight of children.
Do not use after the expiry date.
Do not refrigerate.
The product should be used immediately after opening. Do not use if any particles or discolourations are noticed in the solution. Medicines should not be disposed of via wastewater or household waste. Your doctor or nurse will dispose of any unused medicines. These measures will help protect the environment.

6. FURTHER INFORMATION
What Adenosine 30mg/10ml Solution for Infusion contains
The active ingredient in Adenosine Infusion is adenosine.
Each 10ml contains 30mg of adenosine (3mg/ml). The other ingredients are sodium chloride and water for injection.

What Adenosine 30mg/10ml Solution for Infusion looks like and the contents of the pack
Adenosine Infusion is a clear, colourless solution for infusion.
Adenosine Infusion 30mg/10ml Solution for Infusion is available in packs of 6 single use glass vials.

Marketing Authorisation Holder
Wockhardt UK Ltd, Ash Road North, Wrexham LL13 9UF, UK

Manufacturer
CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF, UK

Other names:
To listen to or request a copy of this leaflet in Braille, large print or audio please call free of charge:
0800 118 5000 (UK only)

Please be ready to give the following information:

Product name
Adenosine 30mg/10ml Solution for Infusion
Reference number
PL 29801/0456

This is a service provided by the Royal National Institute of Blind People.

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Adenosine 30mg/10ml Solution for Infusion
Poland: Adenosine Infusjon Wockhardt
Germany: Adenosin 30mg/10ml Infusionsmittel

Leaflet Prepared:
July 2011
105569/1

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

Marketing Authorisation Number
PL 29801/0456

Date of First Authorisation/Renewal of Authorisation
Date of Revision of Text: July 2011

Pediatric populations:
The safety and efficacy of adenosine in children aged 0–18 years old have not been established. No data is available.

Senior:
See dosage recommendations for adults.

Pharmacological Particulars:
List of excipients
Glycerol acetate
Water for injections

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

Shelf life
Unopened: 26 months.

The product should be used immediately after opening.

Special precautions for storage
Dry, dark, cool.

Nature and contents of container
Clear, resealable, type I glass vial (10ml) sealed with chlorobutyl rubber stopper. Pack of 6 vials packed in a PVC tray in a cardboard carton.
Special precautions for disposal
Do not store above 25°C. Do not incinerate. Do not dispose of any unused product or waste material through the normal waste stream.

105569/1
Module 4
Labelling

**Carton:**

**Vial label:**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Adenosine 30mg/10ml Solution for Infusion (PL 29831/0456; UK/H/4126/002/DC) could be approved. This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany and Poland as Concerned Member States (CMS).

The product is a prescription-only medicine (POM) indicated for use as a coronary vasodilator in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate:

This is an application made according to Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product Adenoscan, 30mg/10ml, Solution for Infusion which was originally granted a licence to Sanofi-Aventis, UK on 03 May 1995.

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.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this products.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 03 August 2011. After a subsequent national phase, the licence was granted in the UK on 01 September 2011.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Adenosine 30mg/10ml Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Adenosine</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other cardiac preparations (C01EB 10)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>30mg/10ml solution for infusion</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised procedure</td>
<td>UK/H/4126/002/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany and Poland.</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0456</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK</td>
</tr>
</tbody>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Adenosine
Chemical name: 9-b-D-Ribofuranosyl-9H-purin-6-amine
Structure:

Molecular formula: C₁₀H₁₃N₅O₄
Molecular mass: 267.2
Appearance: Adenosine is a white or almost white crystalline powder which is slightly soluble in water, soluble in hot water and practically insoluble in ethanol (96%) and methylene chloride. It is sparingly soluble in dilute mineral acids.

Adenosine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance adenosine are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium chloride and Water for Injections.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a product that could be considered a generic medicinal product of the reference product Adenoscan, 30mg/10ml, Solution for Infusion (Sanofi-Aventis, UK).

Details of the pharmaceutical development of the product have been supplied and are satisfactory.

Comparative impurity profiles have been provided for the proposed and originator products.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using pilot scale batches and has shown satisfactory results. The applicant has committed to performing process validation with the first three full-scale batches of the drug product.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in clear, neutral type I glass vials (10ml) sealed with chlorobutyl rubber closures and is available in pack sizes of 6 vials packed in a polyvinylchloride tray in a cardboard carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened product, with the storage conditions ‘Do not refrigerate’. The product should be used immediately after opening.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA form
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of adenosine are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with a currently marketed brand leader, i.e. no increase in environmental burden is anticipated, the justification is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with this application and none is required.

Efficacy
No new efficacy data were submitted and none were required for this application.

Safety
No new safety data were submitted and none were required for this application.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for this application.

Conclusion
There are no objections to the approval of this application from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Adenosine 30mg/10ml Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none were required for an application of this type.

Efficacy
No new efficacy data were submitted and none were required for an application of this type.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with adenosine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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