Public Assessment Report

Decentralised Procedure

ADENOSINE 3MG/ML SOLUTION FOR INJECTION

Procedure No: UK/H/4126/001/DC

UK Licence No: PL 29831/0457

WOCKHARDT UK LTD
On 03 August 2011, Germany, Poland and the UK agreed to grant a Marketing Authorisation to Wockhardt UK Ltd for the medicinal product Adenosine 3mg/ml Solution for Injection (PL 29831/0457; UK/H/4126/001/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) used:
- during a test. This helps doctors find out what type of arrhythmia (uneven heart beat) you have
- to bring your heart back to normal if you have a type of arrhythmia called paroxysmal supraventricular tachycardia (SVT) or Wolff-Parkinson-White Syndrome.

Adenosine 3mg/ml Solution for Injection works by slowing down electrical impulse between the upper and lower chambers of the heart. This slows the heart fast or uneven beat called arrhythmias.

Adenosine 3mg/ml Solution for Injection contains the active ingredient adenosine which belongs to a group of medicines called antiarrhythmics.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Adenosine 3mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.
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### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Adenosine 3mg/ml Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Adenosine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Injection</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>3mg/ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Germany and Poland.</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/4126/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 03 August 2011</td>
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</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Adenosine 3mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 6mg of adenosine per 2ml (3mg/ml).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection (injection).

A clear, colourless solution free from visible particles.

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 (Wolf-Parkinson-White Syndrome).

Diagnostic Indications
Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although adenosine 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 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 intravenous (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 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

Adults:
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
The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available. No controlled paediatric study has been undertaken. Published uncontrolled studies show similar effects of adenosine in adults and children: effective doses for children were between 0.0375 and 0.25mg/kg.

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 injection is contraindicated for patients presenting:

- Known hypersensitivity to adenosine or to any of the excipients.

- 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 injection 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- 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 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 injection. It is therefore suggested that adenosine injection should not be administered to patients receiving dipyridamole; if use of Adenosine Injection is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenosine 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 injection should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Adenosine 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 injection contains approximately 7mg sodium per injection vial (2ml) i.e. essentially ‘sodium-free’.

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 injection should not be administered to patients receiving dipyridamole; if use of adenosine injection is essential, dipyridamole should be stopped 24 hours before hand, or the dose of adenosine should be greatly reduced (see section 4.4).

Aminophylline, theophylline and other xanthines 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 injection.

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 Injection should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Adverse events are ranked under the heading of the frequency:

Very common (>1/10), Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), 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).
## Cardiac Disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Applicable to Adenosine 6mg/2ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>- Bradycardia</td>
</tr>
<tr>
<td></td>
<td>- Sinus pause, skipped beats</td>
</tr>
<tr>
<td></td>
<td>- Atrial extrasystoles</td>
</tr>
<tr>
<td></td>
<td>- Atrio-Ventricular block</td>
</tr>
<tr>
<td></td>
<td>- Ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>- Sinus tachycardia</td>
</tr>
<tr>
<td></td>
<td>- Palpitations</td>
</tr>
<tr>
<td>Very rare</td>
<td>- Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>- Severe bradycardia not corrected by atropine and possibly requiring temporary pacing</td>
</tr>
<tr>
<td></td>
<td>- Ventricular excitability disorders Including ventricular fibrillation and torsade de pointes (see section 4.4)</td>
</tr>
<tr>
<td>Not known</td>
<td>- Hypotension sometimes severe</td>
</tr>
<tr>
<td></td>
<td>- asystole /Cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease /cardiac disorder (see section 4.4)</td>
</tr>
</tbody>
</table>

## Nervous System disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Dizziness, light-headedness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Head pressure</td>
</tr>
<tr>
<td>Very rare</td>
<td>- Transient and spontaneously rapidly reversible worsening of intracranial hypertension</td>
</tr>
<tr>
<td>Not known</td>
<td>- Loss of consciousness / syncope</td>
</tr>
<tr>
<td></td>
<td>- Convulsions, especially in predisposed patients (see section 4.4)</td>
</tr>
</tbody>
</table>

## Eye disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Blurred vision</td>
</tr>
</tbody>
</table>

## Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Dyspnea (or the urge to take a deep breath)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>- Hyperventilation</td>
</tr>
<tr>
<td>Very rare</td>
<td>- Bronchospasm (see section 4.4)</td>
</tr>
<tr>
<td>Not known</td>
<td>- Respiratory failure (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>- Apnea / Respiratory arrest,</td>
</tr>
</tbody>
</table>

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

## Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Nausea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>- Metallic taste</td>
</tr>
<tr>
<td>Not known</td>
<td>- Vomiting</td>
</tr>
</tbody>
</table>

## Vascular disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Flushing</td>
</tr>
</tbody>
</table>
## Adenosine 3mg/ml Solution for Injection

### 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

ATC Code: Other Cardiac Preparations C01EB 10

Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect

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 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.

#### 5.2 Pharmacokinetic properties

It is impossible to study adenosine in classical pharmacokinetic studies. 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 less than 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 that are additional to those already included in other sections of the SPC.
6  PHARMACEUTICAL PARTICULARS
6.1 List of excipients
   Sodium chloride
   Water for injections

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

6.3 Shelf life
   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 (2ml) 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 29831/0457

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

10 DATE OF REVISION OF THE TEXT
    01/09/2011
PAR Adenosine 3mg/ml Solution for Injection

UK/H/4126/001/DC

Module 3

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

The name of your medicine is Adenosine Injection. The active ingredient in your medicine is adenosine. Adenosine belongs to a group of medicines called antiarrhythmics. Adenosine Injection works by slowing down electrical impulse between the atria and lower chambers of the heart. This slows the heart fast or uneven heart beat called arrhythmias. Adenosine Injection is used:

- during a test. This helps doctors find out what type of arrhythmia (irregular heartbeat) you have
- to bring your heart back to normal if you have a type of arrhythmia called paroxysmal supraventricular tachycardia (PVT) or Wolff-Parkinson-White Syndrome.

2. BEFORE YOU ARE GIVEN ADENOSINE INJECTION

Do not take Adenosine Injection if you:

- are allergic (hypersensitive) to adenosine or to any of the other ingredients in this medicine (see section 6. Further information). Signs of an allergic reaction include: rash, swelling or breathing problems, swelling of your lips, face, throat or tongue
- have problems with your heart rhythm and do not have a pacemaker (second or third degree Atrioventricular block, sick sinus syndrome)
- have very low blood pressure (severe hypotension)
- have subarachnoid or any other severe breathing problems
- have a type of heart failure where your heart is not pumping out enough blood
- have been told you have ‘Long QT syndrome’. This is a rare heart problem that can lead to a fast heart beat and fainting.

Do not have this medicine if any of the above applies to you, if you are not sure, talk to your doctor, nurse before you are given Adenosine.

Take special care with Adenosine Injection if you have:

- low blood volume which is not corrected by medicines
- narrowing of your left main artery supplying blood to your heart (left main coronary stenosis)
- been told that you have a heart problem whereby the electrical impulses in parts of your heart take longer than normal to discharge and then re-charge (prolonged QT interval

3. HOW YOU WILL BE GIVEN ADENOSINE INJECTION

Adenosine Injection is a medicine for use in hospitals. Adenosine Injection will be given to you by a doctor or nurse as an injection. The injection will be in one of your veins. Your heart rate and blood pressure will be closely monitored.

4. POSSIBLE SIDE EFFECTS

The possible side effects (adverse reactions) with Adenosine Injection are:

- 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 (stenotic valvular heart disease)
- a left-right shunt 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
- inflammation of the membrane surrounding your heart (pericarditis) or a build up of the fluid around your heart (pericardial effusion)
- had severe heart failure
- had a heart attack or if you have had a heart transplant in the last year
- any allergy problem with your heart (first degree Atrioventricular block or a bundle branch block). These conditions may be temporarily aggravated when you are given Adenosine Injection

5. URBAN THREATS

- an unusual heart rhythm, for example your heartbeat is very fast or uneven (atrial fibrillation or atrial flutter)

6. FURTHER INFORMATION

- difficulty in breathing (bronchospasm)
- ever had fits or convulsions.

If you get a very slow heartbeat (bradycardia), respiratory failure, a heart problem that can be fatal (asystole), severe chest pain (angina) or very low blood pressure (severe hypotension), treatment with Adenosine should be avoided. If you are not sure if any of the above applies to you, talk to your doctor or nurse before being given Adenosine Injection.

Adenosine Injection is not recommended for use in children.

Taking other medicines

Please tell your doctor if you are taking or have recently taken other medicines, including medicines obtained without a prescription. The following medicines can affect or be affected by treatment with Adenosine Injection:

- diprindolamine (a medicine used to thin the blood). Make sure you tell your doctor you are taking diprindolamine. Your doctor may decide you should not have Adenosine Injection or may tell you to stop taking diprindolamine 24 hours before you are given Adenosine Injection or may give you a lower dose of Adenosine Injection
- amiodarone or thalidomide (medicines used to help breathing). Your doctor may tell you to stop taking it 24 hours before you are given Adenosine Injection
- caffeine (sometimes found in headache medicines)

Taking Adenosine Injection with food and drink

Food and drink containing xanthines for example tea, coffee, chocolate and cola, should be avoided for at least 12 hours before you are given Adenosine Injection.

Pregnancy and breast-feeding

Talk to your doctor or nurse before having this medicine if:

- You are pregnant, might become pregnant, or think that you may be pregnant. You should not be given Adenosine Injection if you are pregnant or think you may be pregnant, unless clearly necessary
- You are breast-feeding. You should not be given Adenosine Injection if you are breast-feeding

Ask your doctor or nurse for advice before taking any medicine.

Important information about some of the ingredients of Adenosine Injection

This medicinal product contains approximately 7mg sodium per vial (2ml) i.e. essentially ‘sodium free’.

Posology and Method of Administration

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

Method of administration

It should be administered by rapid intravenous (IV) bolus injection according to the ascending dosage schedule below. To be certain the solution reaches the myocardial circulation administer either directly into a vein or into an IV line. If given into an IV line it should be injected as promptly as possible, and followed by a rapid saline flush.

Adenosine 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

Adults

Initial dose: low given as a rapid intravenous bolus (over 2 seconds). Second dose: If the first dose does not result in elimination of the supraventricular tachycardia, additional doses of 15 mg given at 20 second intervals, should be given 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. 60 mg should be given as a rapid intravenous bolus.
PAR Adenosine 3mg/ml Solution for Injection
UK/H/4126/001/DC

1. ADULTS

The first dose is 3mg given over 2 seconds. This is given as a rapid injection into your vein.

If the first dose does not bring your heart beat to normal then you will be given a second dose. The second dose will be 6mg given as a rapid injection.

If the second dose does not bring your heart rate to normal then you will be given a third dose. The third dose is 12mg given as a rapid injection.

You will not be given any more doses after the 12mg dose.

Children

Your child’s doctor will decide if this medicine is needed and how much should be given.

If you have more Adenosine Injection than you should

This medicine is given by your doctor or nurse. It is unlikely that you will be given too much. Your doctor will carefully work out how much Adenosine injection you should be given.

If you have more of this medicine than you should, the following effects may happen:

- **very low blood pressure** (severe hypotension)
- **slow heartbeat** (bradycardia)
- **a heart problem called atrioventricular block**

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 injection would quickly stop when the infusion is stopped. You may be given an injection of a medicine called atropine 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 injection can cause side effects, although not everybody gets them.

The following side effects may be experienced when taking Adenosine Injection. If any of the side effects get worse, tell your doctor or nurse and they may stop the injection.

The side effects normally settle within seconds or minutes after the injection is finished but you should tell your doctor or nurse if any of them happen.

**Very common** (affects more than 1 person in 100):

- slow heartbeat (bradycardia)
- skipped heartbeats or extra heart beats
- a heart problem called atrioventricular block where the heart's start to beat slowly
- feeling a heart attack is about to happen
- feeling negative
- nausea feeling sick
- unusual side effects, such as burning.

**Uncommon** (affects less than 1 person in 100):

- feeling pressure in your head or a headache
- blurred vision
- metallic taste in your mouth
- feeling a heart attack is about to happen
- nausea feeling sick
- unusual side effects, such as burning.

**Rare side effects** (affect less than 1 person in every 10,000):

- severe bradycardia (very slow heartbeat)
- very slow, fast or uneven heartbeats
- severe breathlessness or problems in breathing
- redness, pain or swelling at the site of injection
- feeling uncomfortable during injection
- worsening of high blood pressure that affects the brain (hypertensive encephalopathy).

**Frequency not known:**

- loss of consciousness or fainting
- vomiting (feeling sick)
- convulsions
- low blood pressure
- your heart does not work properly to circulate blood around your body (cardiac arrest).
- a severe heart problem, where the heart stops pumping blood around the body (asystole).
- your lungs do not work properly to provide enough oxygen to your blood
- stopping breathing (respiratory arrest).

If any of the 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 INJECTION

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 discolouration 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 medicine. These measures will help protect the environment.

6. FURTHER INFORMATION

What Adenosine 3mg/ml (6mg in 2ml) Solution for Injection contains

- The active ingredient is adenosine.
- Each 2ml contains 6mg of adenosine.
- The other ingredients are sodium chloride and water for injections.

What Adenosine 3mg/ml (6mg in 2ml) Solution for Injection looks like and the contents of the pack

Adenosine 3mg/ml (6mg in 2ml) Solution for Injection is available in packs of 6 single use glass vials.

Marketing Authorisation Holder

WOCKHARDT UK Ltd, Ash Road North, Wrexham LL13 9UF, UK

Manufacture

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

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK only). Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product name</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine 3mg/ml</td>
<td>29851/0407</td>
</tr>
<tr>
<td>(6mg in 2ml) Solution for injection</td>
<td></td>
</tr>
</tbody>
</table>

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

This medicinal product is authorised in the Member States of the EEA under the following names:

- UK: Adenosine 3mg/ml Solution for Injection
- Poland: Adenosine Injection Wockhardt
- Germany: Adenosin 3mg/ml injectionlösung

Leaflet Prepared: July 2011.

105565/1

Additional or higher doses are not recommended.

Paediatric population:

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

Published uncontrolled studies show similar effects of adenosine in adults and children; effective doses for children were between 0.0375 and 0.25mg/kg.

Elderly:

See dosage recommendations for adults.

Diagnostic dose

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

Method of administration: Rapid intravenous injection only.

Pharmaceutical particulars

List of Excipients
Sodium chloride
Water for injections

Incompatibilities

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

Shelf Life
Unopened: 24 months.

The product should be used immediately after opening.

Special precautions for storage
Do not refrigerate.

Nature and contents of container
Clear, neutral type I glass vials (2ml) sealed with chlorobutyl rubber closures. Packs of 6 vials packed in a PVC tray in a cardboard carton.

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.

Marketing Authorisation Holder

WOCKHARDT UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Marketing Authorization Number
PL. 59831/0407

Date of First Authorisation/Renewal of Authorisation
105565/1

Date of Revision of Text
July 2011
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 3mg/ml Solution for Injection (PL 29831/0457; UK/H/4126/001/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:

Therapeutic indications
- for rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome).

Diagnostic indications
- as an aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although adenosine injection will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity.
- for sensitisation of intra-cavitary electrophysiological investigations.

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 Adenocor, 3mg/ml (6mg in 2ml), solution for Injection which was originally granted a licence to Sanofi-Aventis, UK on 17 September 1993.

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 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.

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 3mg/ml Solution for Injection</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other cardiac preparations (C01EB 10)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>3mg/ml solution for injection</td>
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<tr>
<td>Reference numbers for the Decentralised procedure</td>
<td>UK/H/4126/001/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany and Poland.</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0457</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK</td>
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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: C_{10}H_{13}N_{5}O_{4}
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 Adenocor, 3mg/ml (6mg in 2ml), solution for Injection (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 (2ml) 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 3mg/ml Solution for Injection 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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