Caden™ 6 mg / 2 ml

[Adenosine]

Solution for injection

Pharma Bavaria International

1. Name of the medicinal product

Caden 6 mg/2 ml solution for injection

2. Qualitative and quantitative composition

Each ml of solution for injection contains 3 mg of adenosine
One vial of 2 ml contains 6 mg of adenosine (3 mg/ml).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.
Clear colourless solution

4. Clinical particulars

4.1 Therapeutic indications

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

Diagnostic indications
Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although Caden will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of atrioventricular (AV) conduction helps diagnosis of atrial activity. Sensitisation of intra-cavitary electrophysiological investigations.

4.2 Posology and method of administration

Caden is intended for hospital use only with monitoring and cardiorespiratory resuscitation equipment available for immediate use.

It should be administered by rapid intravenous 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 intravenous line.

If given into an intravenous line it should be injected as proximally as possible and followed by a rapid saline flush.

Caden 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.

Therapeutic dose

Adults
Initial dose: 3 mg 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, 6 mg 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, 12 mg 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. The level of evidence does not allow a recommended posology.

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

Caden is contraindicated for patients presenting:

- Known hypersensitivity to the adenosine or any of the excipients listed in section 6.1
- Sick sinus syndrome, second or third degree Atrio-Ventricular (AV) block (except in patients with a functioning artificial pacemaker)
- Chronic obstructive lung disease with evidence of bronchospasm (e.g. asthma, bronchiale)
- Long QT syndrome
- Severe hypotension
- Decompensated states of heart failure

4.4 Special warnings and precautions for use

Special warnings

Due to the possibility of transient cardiac arrhythmias arising during conversion of the supraventricular tachycardia to normal sinus rhythm, administration should be carried out in 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 (see section 4.2).

Because it has the potential to cause significant hypotension, adenosine should be used with caution in patients with left main coronary stenosis, uncorrected hypovolemia, stenotic valvular heart disease, left to right shunt, pericarditis or pericardial effusion, autonomic dysfunction or stenotic carotid artery disease with cerebrovascular insufficiency.

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

Adenosine should be used with caution in patients with atrial fibrillation or flutter and especially in those with an accessory by-pass tract since particularly the latter may develop increased conduction down the anomalous pathway.

Rare cases of severe bradycardia have been reported. Some occurred in early post heart transplant patients; in the other cases, occult sino-atrial disease was present. The occurrence of severe bradycardia should be taken as a warning of underlying disease and could potentially favour the occurrence of torsades de pointes, especially in patients with prolonged QT intervals.

In patients with recent heart transplantation (less than 1 year) an increased sensitivity of the heart to adenosine has been observed.

Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, Caden'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 Caden. It is therefore suggested that Caden should not be administered to patients receiving dipyridamole; if use of Caden is essential, dipyridamole should be stopped 24 hours beforehand, or the dose of Caden should be greatly reduced. (see section 4.5 Interactions with other Medicines 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, Caden should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Caden 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).

Caden contains 3.54 mg sodium per ml (7.08 ml/2 ml vial). 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. Asystole has been reported following concomitant administration. It is therefore suggested that adenosine should not be administered to patients receiving dipyridamole; if use of Caden is essential, dipyridamole should be stopped 24 hours beforehand, or the dose of Caden should be greatly reduced (see section 4.4.).

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

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

Caden may interact with drugs tending to impair cardiac conduction.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited 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. Caden should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse reactions are ranked under 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).

Nervous System disorders
Common: Headache, dizziness/light-headedness
Uncommon: Head pressure
Very rare: Transient and spontaneously and rapidly reversible worsening of intracranial hypertension
Not known: Loss of consciousness/syncope, convulsions, especially in predisposed patients (see section 4.4)

Psychiatric disorders
Common: Apprehension

Cardiovascular Disorders
Very common: Bradycardia, asystole, sinus pause, atrioventricular block, atrial extrasystoles, skipped beats, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia
Uncommon: Sinus tachycardia, palpitations
Very rare: Severe bradycardia which is not corrected by atropine and possibly requiring temporary pacing, atrial fibrillation, ventricular excitability disorders including ventricular fibrillation and torsade de pointes (see section 4.4)
Not known: Asystole/cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease/cardiac disorder (see section 4.4), MI/ST segment elevation especially in patients with pre-existing severe CAD (see section 4.4.)

Eye disorders
Uncommon: Blurred vision

Gastrointestinal system disorders
Common: Nausea
Uncommon: Metallic taste
Not known: Vomiting

Respiratory, thoracic and mediastinal disorders
Very common: Dyspnea (or the urge to take a deep breath)
Uncommon: Hyperventilation
Very rare Bronchospasm (see section 4.4), apnea/respiratory arrest
Cases of respiratory failure, bronchospasm, apnea, and respiratory arrest with fatal outcome have been reported.

Vascular disorders
Very common: Flushing
Not known: Hypotension sometimes severe, cerebrovascular accident/ transient ischemic attack; secondary to the hemodynamic effects of adenosine including hypotension (see Warnings and Precautions)

Immune system disorders
Not known: Anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash)

General disorders and administration site conditions
Very common: Chest pressure/pain, feeling of thoracic constriction/ oppression
Common: Burning sensation
Uncommon: Sweating, feeling of general discomfort/weakness/pain
Very rare: Injection site reactions

4.9 Overdose

Overdose 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 of adenosine, and that therapeutic concentrations of theophylline block its exogenous effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: Other Cardiac Preparations CO1EB10.

Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect.

Antiarrhytmic 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, Caden (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

Adenosine is impossible to study via classical ADME protocols. Adenosine 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 which are additional to that already included in other sections.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride and 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

3 years.
Any portion of the vials not used at once should be discarded.

6.4 Special precautions for storage

Store at or below 30 °C. Do not refrigerate.

6.5 Nature and contents of container

Pack of 6 type I glass vials, containing 2ml of 3 mg/ml solution, corresponding to 6 mg of adenosine per vial. Each vial is sealed with chlorobutyl stoppers and aluminium flip-off seal caps with bordeaux colored polypropylene disks.

6.6 Special precautions for disposal and other handling

Caden is ready to use.

There are no special requirements for disposal.

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

7. Product owner

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8. Product registrant

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9. Product registration number

SIN16391P

10. Date of revision of the text

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