SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICNAL 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).
Excipients with known effect
Sodium – 7,08 mg per vial (as sodium chloride).
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 narrow complex supraventricular tachycardias. Although Caden is not effective in the conversion of 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, if necessary.

Method of administration
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 to the catheter 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.

Posology

Adults:
Initial dose: 3 mg given as a rapid intravenous bolus (over 2 seconds).
2nd dose: if the 1st 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.
3rd dose: if the 2nd 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.

Administration of additional or higher doses than those referred above is not recommended.

Paediatric population
During administration of adenosine cardio-respiratory resuscitation equipment must be available for immediate use if necessary.
Adenosine is intended for use with continuous monitoring and ECG recording during administration.

The dosing recommended for the treatment of paroxysmal supraventricular tachycardia in the paediatric population is:

- Initial dose of 0.1 mg/kg body weight (maximum dose of 6 mg);
- Incremental doses of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia (maximum dose of 12 mg).

Method of administration
Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an intravenous line. If given into an intravenous line it should be injected through as proximally as possible to the catheter and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used.

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:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second or third degree Atrio-Ventricular (AV) block, sick sinus syndrome, except in patients with a functioning artificial pacemaker.
- Long QT syndrome.
- Severe hypotension.
- 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 hospital use only with monitoring and cardiorespiratory 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, Caden 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.

Caden infusion should be discontinued in any patient who develops persistent or symptomatic hypotension.
Caden should be used with caution in patients with recent myocardial infarction, severe heart failure.
Caden should be used with caution in patients with minor conduction defects (first degree AV block, bundle branch block) that could be transiently aggravated during infusion.

Caden 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.

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, its dose should be reduced. (see section 4.5).

Precautions:

The occurrence of respiratory failure (potentially fatal), asystole/cardiac arrest (potentially fatal), angina, severe bradycardia or hypotension should lead to immediate discontinuation of administration.

Adenosine may trigger convulsions in patients who are susceptible to convulsions. In those patients, the administration of Caden 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.

Paediatric population

Adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome. See section 5.1.

The efficacy of intraosseus administration has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Dipyridamole, known as an inhibitor of adenosine uptake, may potentiate the action of Caden; in a study dipyridamole was shown to produce a 4 fold increase in adenosine actions. 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 before hand, or the dose of Caden 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 Caden.

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

Adenosine may interact with drugs tending to impair cardiac conduction.
Paediatric population
Interaction studies were only performed in adults.

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 (see section 5.3).

Caden is not recommended during pregnancy and in women of reproductive age who do not use contraceptive methods, unless the physician considers the benefits to outweigh the potential risks.

Breast-feeding
It is unknown whether adenosine is excreted in human milk. Caden should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100; <1/10), uncommon (≥1/1,00; <1/100), rare (≥1/10000; <1/1000), very rare (<1/10000), not known (cannot be

estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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).

Table 1

System organ class	Adverse reactions
Cardiac Disorders	
Very common	- Bradycardia - Sinus pause, skipped beats - Atrial extrasystoles - Atrio-Ventricular block - Ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia
Uncommon	- Sinus tachycardia - Palpitations
Very rare	- Atrial fibrillation - Severe bradycardia not corrected by atropine and possibly requiring temporary pacing - Ventricular excitability disorders, including ventricular fibrillation and torsade de pointes (see section 4.4)
Not known	- Hypotension sometimes severe - Asystole/cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease/cardiac disorder (see section 4.4) - Arteriospasm coronary which may lead to myocardial infarction.
Nervous System disorders	
Common	- Headache - Dizziness, light-headedness
Uncommon	- Head pressure
Very rare	-Transient and spontaneously rapidly reversible worsening of intracranial hypertension
Not known	- Loss of consciousness/syncope - Convulsions, especially in predisposed patients (see section 4.4)
Eye disorders	
Uncommon	- Blurred vision
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)
Not known	- Respiratory failure (see section 4.4)

	- Apnea/Respiratory arrest
	Cases of respiratory failure, bronchospasm, apnea, and respiratory arrest with fatal outcome have been reported.
Gastrointestinal disorders	
Common	- Nausea
Uncommon	- Metallic taste
Not known	- Vomiting
Vascular disorders	
Very common	- Flushing
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
Psychiatric disorders	
Common	- Apprehension

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems' to the respective national regulatory authorities

4.9 Overdose

No cases of overdose have been reported. As the half-life of adenosine in blood is very short, it is assumed that the duration of any side effect is very limited.

Pharmacokinetic evaluation indicates that methyl xanthines are competitive antagonists to adenosine, and that therapeutic concentrations of theophylline block its exogenous effects.

Administration of IV aminophylline or theophylline may be needed.

5. PROPRIEDADES FARMACOLÓGICAS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.2.5 - Cardiovascular apparatus. Antiarrhythmics. Others Antiarrhythmics, ATC code:CO1EB10.

Endogenous nucleoside with peripheral vasodilator/antiarrhythmic effect. 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 Caden can aid the diagnosis of complex tachycardias.

Caden 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.

Paediatric population
No controlled studies have been conducted in paediatric patients with adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, the safety and efficacy of adenosine in children aged 0 to 18 years with PSVT is considered established based on extensive clinical use and literature data (open label studies, case reports, clinical guidelines).

Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years. Studies were heterogenic in terms of age and dosing schedules. SVT was terminated in 72 to 100% of cases in most of the published studies. Dosages used varied from 37.5mcg/kg to 400mcg/kg. Several studies discussed a lack of response to starting doses less than 100mcg/kg.

Depending on the child's clinical history, symptoms and ECG diagnosis, adenosine has been used in clinical practice under expert supervision in children with stable wide-QRS complex tachycardia and Wolff-Parkinson- White syndrome; however, the currently available data does not support a paediatric indication. In total, 6 cases of adenosine-induced arrhythmias (3 atrial fibrillation, 2 atrial flutter, 1 ventricular fibrillation) have been described in 6 children aged 0 to 16 years with manifest or concealed WPW syndrome, of which 3 spontaneously recovered and 3 needed amiodarone +/- cardioversion (see also section 4.4).

Adenosine has been used as an aid to diagnosis of broad or narrow complex supraventricular tachycardias in same doses as for treatment of supraventricular tachycardia. Although adenosine will not convert atrial flutter, atrial

fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity. However, the currently available data does not support a paediatric indication for the use of adenosine for diagnostic purposes.

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

As adenosine is naturally present in all living cells, no animal studies have been performed to evaluate the carcinogenic potential of Caden (adenosine). No controlled reproductive studies were conducted in animals with adenosine.

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

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.
Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

Pharma Bavaria Internacional (PBI) Portugal, Unipessoal, Lda
Viela da Beloura, nº 6, Lj 19
2710-693 Sintra
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

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