SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Adenohardt

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 6 mg of adenosine per 2 ml (3 mg/ml).
Excipient(s) with known effect

Each 2 ml vial contains 7.08 mg (3.56 mg/ml) of sodium equivalent to 0.3 mmol (0.15 mmol/ml) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colorless 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 (Wolff-Parkinson-White Syndrome).

4.2 Posology and method of administration

Adenohardt 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 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.
Adenohardt 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.

Children

The level of evidence does not allow a recommended posology.

Elderly

See dosage recommendations for adults.

Hepatic/Renal impairment

As adenosine requires no hepatic or renal function for its activation or inactivation, hepatic and/or renal failure would not be expected to alter efficacy or tolerance.

4.3 Contraindications

Adenohardt is contraindicated for patients presenting:

- Hypersensitivity to the active substance or to 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 bronchial)
- 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 (*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. There have been reports of cerebrovascular accident/transient ischemic attack, secondary to the haemodynamic effects of adenosine.

There have been reports of myocardial infarction shortly after use of Adenohardt.
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-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, Adenohardt'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 Adenohardt. It is therefore suggested that Adenohardt should not be administered to patients receiving dipyridamole. If use of Adenohardt is essential, dipyridamole should be stopped 24 hours, or the dose of adenosine should be greatly reduced (*see section 4.5*).

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, Adenohardt should be used with caution in patients with a prolonged QT interval, whether this is drug-induced or of metabolic origin.
Adenohardt 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*).

Adenohardt contains less than 1 mmol sodium (23 mg) per injection vial (2 ml), that is to say. 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 Adenohardt should not be administered to patients receiving dipyridamole. If use of Adenohardt 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.
Adenohardt may interact with drugs tending to impair cardiac conduction.

4.6 Fertility, pregnancy and breastfeeding

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.
Breastfeeding
It is unknown whether adenosine metabolites are excreted in human milk.
Adenohardt should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

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).

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).

- **Immune system disorders**

Not known: anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash)

- **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: asystole/cardiac arrest, sometimes fatal especially in patients with underlying ischaemic heart disease/cardiac disorder (*see section 4.4*), arteriospasm coronary which may lead to myocardial infarction.

- **Vascular disorders**

Very common: flushing

Not known: hypotension (sometimes severe) (*see section 4.4*)

- **Nervous system disorders**

Common: headache, dizziness, light-headedness, paraesthesia

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: dyspnoea (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*), apnoea/respiratory arrest

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

- **Gastrointestinal disorders**

Common: nausea

Uncommon: metallic taste

Not known: vomiting

- **Psychiatric disorders**

Common: nervousness

- **General disorders and administration site conditions**

Very common: chest pain or pressure, feeling of thoracic constriction/oppression

Uncommon: sweating, discomfort in the leg, arm or back, feeling of general discomfort, weakness/pain

Very rare: injection site reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiovascular system, cardiac therapy, other cardiac preparations.
ATC Code: C01EB10

Mechanism of action

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, Adenohardt (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. It is present in various forms in all cells of the body where it plays an important role in energy production and utilization 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 <10 seconds. The *in vivo* half-life may be even shorter.

5.3 Pre-clinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that 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

The expiry date is indicated on the packaging materials.

6.4 The product should be used immediately after opening. Special precautions for storage

Store below 25°C. Do not refrigerate.

6.5 Nature and contents of container

Clear, neutral type I glass vial containing 2 ml of solution. Each vial is

sealed with chlorobutyl rubber closures. Packs of 6 vials packed in a PVC tray in a cardboard carton.

6.6 Special precautions for disposal and other handling

The product is for single use only. Any portion of the vial, not used at once, should be discarded. The product should be inspected visually for particulate matter and colouration prior to administration. Where the visual appearance of the product may have changed, the vial should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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

8. LICENSE HOLDER

Propharm Ltd. P.O.Box 4046, 23 Ben-Gurion street, Zichron Yaacov 30900.

9. LICENSE NUMBER

157-77-34595-00

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