

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Adcus 3mg/ml Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 3mg of adenosine.  
Each vial contains 30mg of adenosine per 10ml of solution (3mg/ml).  
It also contains 3.54mg (0.15mmol) of sodium per 1ml of solution.  
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for infusion (infusion).  
Clear, colourless solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Intravenous (IV) Adcus 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.  
Adcus is indicated in adults.

### 4.2 Posology and method of administration

Adcus is intended for use in hospitals. It should be administered following the same procedure as for exercise testing, where facilities for cardiac monitoring and cardio-respiratory resuscitation are available for immediate use, if necessary. During administration of Adcus, continuous electrocardiogram (ECG) control is necessary, as life-threatening arrhythmia might occur. Heart rate and blood pressure should be monitored every minute.

Adults:

1. Adcus 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 Adcus and radionuclide administration are recommended to avoid an adenosine bolus effect.
2. After three minutes of infusion of Adcus, 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 infusion of Adcus.
3. To avoid an adenosine bolus effect, blood pressure should be measured in the arm opposite to the infusion of Adcus.

The table below is given as a guide for adjustment of the infusion rate of undiluted Adcus, in line with bodyweight (total dose 0.84 mg/kg).

Patient Weight (kg)	Infusion Rate (ml/min)
45 - 49	2.1
50 - 54	2.3
55 - 59	2.6
60 - 64	2.8

65 - 69	3.0
70 - 74	3.3
75 - 79	3.5
80 - 84	3.8
85 - 89	4.0
90 - 94	4.2
95 - 99	4.4
100 - 104	4.7

**Paediatric population:**

The safety and efficacy of Adcus in children aged 0 to 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

**Elderly:**

See dosage recommendations for adults.

**4.3 Contraindications**

Adcus is contra-indicated in patients suffering from:

- 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
- 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**

Adcus 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 (*see section 4.2*).

Because it has the potential to cause significant hypotension, Adcus 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. Adcus should be discontinued in any patient who develops persistent or symptomatic hypotension.

Adcus should be used with caution in patients with recent myocardial infarction or severe heart failure. Adcus 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.

Adenosine may trigger convulsions in patients who are susceptible to convulsions.

Adcus 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*).

Adcus contains 9mg sodium chloride per 1ml (corresponding to 3.54mg of sodium (0.15mmol) per 1ml of solution). 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 Adcus. In one study, dipyridamole was shown to produce a 4 fold increase in adenosine actions. It is therefore suggested that Adcus should not be administered to patients receiving dipyridamole; if use of Adcus is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adcus should be greatly reduced.

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

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

Adcus 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. Adcus 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 (≥1/1000, <1/100), Rare (≥1/10 000, <1/1000), Very rare (<1/10 000), Not known (cannot be estimated from available data).

Cardiac Disorders	
Common	Hypotension, sometimes severe ( <i>see section 4.4</i> ), Atrio-Ventricular block ( <i>see section 4.4</i> ), ST segment depression on ECG, sustained or non-sustained ventricular tachycardia  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 ( <i>see section 4.4</i> )
Not known	Sinus tachycardia, atrial fibrillation, ventricular fibrillation, asystole/cardiac arrest (sometimes fatal, especially in patients with underlying ischemic heart disease/cardiac disorder, ( <i>see section 4.4</i> ))
<b>Nervous System disorders</b>	
Very common	Headache
Common	Dizziness/Lightheadedness Paresthesia
Rare	Tremor, drowsiness
Not known	Loss of consciousness/syncope Convulsions, especially in predisposed patients ( <i>see section 4.4</i> )
<b>Eye disorders</b>	
Rare	Blurred vision
<b>Ear and labyrinth disorders</b>	
Rare	Tinnitus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very common	Dyspnea (or the urge to take a deep breath)
Rare	Bronchospasm ( <i>see section 4.4</i> ) Nasal congestion
Very rare	Respiratory failure ( <i>see section 4.4</i> )
Not known	Apnea/Respiratory arrest
Cases with fatal outcome of respiratory failure, of bronchospasm, and of apnea/respiratory arrest have been reported.	
<b>Gastrointestinal disorders</b>	
Very common	Abdominal discomfort
Common	Dry mouth
Uncommon	Metallic taste
Not known	Nausea, vomiting
<b>Renal and Urinary disorders</b>	
Rare	Urinary urgency
<b>Vascular disorders</b>	
Very common	Flushing
<b>General disorders and Administration Site conditions</b>	
Very common	Chest pressure/pain, 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
<b>Reproductive system and breast disorders</b>	
Rare	Nipple discomfort
<b>Psychiatric disorders</b>	
Uncommon	Nervousness

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRa Pharmacovigilance Section, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: <http://www.hpra.ie/>; E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

**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 Adcus (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: C01EB10**

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 A<sub>1</sub> and A<sub>2</sub> 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 A<sub>2</sub> 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 Adcus 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 Adcus.

The increase in blood flow caused by Adcus in normal coronary arteries is significantly more than that in stenotic arteries. Adcus 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 Adcus 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.

#### Paediatric population

Literature review identified three studies where intravenous adenosine infusion was used in conjunction with radionuclide myocardial perfusion imaging at a dose of 0.14mg/kg body weight/min for 2-4 minutes in paediatric patients aged 1 month to 18 years. The largest study included 47 patients aged 1 month to 18 years of age and reported 87% sensitivity (CI 52-97%) and 95% specificity (CI 79-99%) for cardiovascular magnetic resonance imaging under pharmacological stress with intravenous adenosine in a dose of 0.14mg/kg/min for 3 minutes. No adverse events were reported in the study. However, the currently available data is considered very limited to support the use of adenosine for diagnostic purposes in the paediatric population.

## **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 Adcus should be unaffected by hepatic or renal insufficiency.

## **5.3 Preclinical safety data**

Because adenosine is naturally present in all living cells, studies in animals to evaluate the carcinogenic potential of Adenosine 30mg/10ml Solution for Infusion have not been performed.

No controlled 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: 3 years

Once opened, the product should be used immediately.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Colourless, transparent Ph Eur Type I glass vial containing 10ml of solution. Each vial is closed with a chlorobutyl rubber closure and secured with an aluminium cap.

Pack size: 6 x 10ml vials.

## **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 MARKETING AUTHORISATION HOLDER**

Focus Pharmaceuticals Ltd  
Capital House, 1st Floor  
85 King William Street  
London EC4N 7BL  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA1338/007/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 11<sup>th</sup> January 2013

## **10 DATE OF REVISION OF THE TEXT**

August 2015