

IPAR
Public Assessment Report
Scientific discussion

Adcus 3 mg/ml Solution for Infusion
(Adenosine)

IE/H/239/01/DC

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This module reflects the scientific discussion for the approval of Adenosine 3 mg/ml Solution for Infusion. The procedure was finalised 06th November 2012. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Adcus 3mg/ml Solution for Infusion from Focus Pharmaceuticals Ltd..

The product is indicated for:

Adcus 3mg/ml Solution for Infusion is indicated in adults

Intravenous (IV) Adcus 3mg/ml Solution for Infusion 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.

A comprehensive description of the indications and posology is given in the SmPC.

II QUALITY ASPECTS

II.1 Introduction

This application is for Adcus 3 mg/ml Solution for Infusion packaged in a 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. It contains Adenosine as the active substance. The excipients are sodium chloride and water for injections.

II.2 2.2 Drug Substance

The drug substance Adenosine, is a well established active substance. It is described in the European Pharmacopoeia (Ph.Eur.). The Active Substance Master File (ASMF) procedure is followed for the drug substance.

Synthesis of the drug substance has been satisfactorily described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient.

The active substance specification is considered adequate to control the quality and meets the current requirements (they are in line with the requirements of the Ph. Eur. Monograph for Adenosine). Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

The container is suitable and provides adequate protection to the active substance.

Stability studies under ICH conditions have been conducted. Based on the stability data presented 5 years re-test period has been set.

II.3 Medicinal Product

II.3.1 Composition

The Drug Product is presented as a sterile, clear, colourless solution for use as intravenous infusion only. It contains 3 mg per ml (30 mg per 10 ml) of the active substance Adenosine. The excipients are sodium chloride and water for injections. The product is packaged in a colourless, transparent Ph Eur Type I glass vial containing 10 ml of solution. Each vial is closed with a chlorobutyl rubber closure and secured with an aluminium cap. The product is for single use only. Any portion of the vial, not used at once, should be discarded.

II.3.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The purpose of the development was to develop a stable product essentially similar to the

reference product Adenoscan 3mg/ml Solution for Infusion. Comparative analysis with the reference product on the EEA Market demonstrated essential similarity.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated. The results show good production performance throughout production. All tests meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

II.3.4 Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the relevant European guidelines and the standard requirements associated with parenteral preparations. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is presented in a colourless, transparent Ph Eur Type I glass vial containing 10 ml of solution. Each vial is closed with a chlorobutyl rubber closure and secured with an aluminium cap. The excipients are sodium chloride and water for injections. The packaging material complies with the relevant European guidelines.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC). Once open the product should be used immediately (see the SPC for further information).

II.3.8 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Adcus 3 mg/ml Solution for Infusion.

III NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Adenosine are well known. The reference medicinal product for this application is Adenoscan. Given that the active and the excipients in the generic product are essentially similar to the reference product, the pharmacological and toxicological profile of the original molecule can be applied to the generic product. An extensive overview based on literature review and the current SPC for Adenoscan is considered to be sufficient and appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Adcus 3 mg/ml Solution for Infusion is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV CLINICAL ASPECTS

IV.1 Introduction

The present application is made under article 10(1) of Directive 2001/83/EC as amended, i.e.

Adcus 3mg/ml Solution for Infusion is a generic version of the already approved reference product Adenoscan Solution for Infusion by Sanofi Aventis which has been marketed in the EU for more than 10 years. Date of authorisation in UK is 03/05/1995. Consequently, adenosine can be considered as a well-established drug.

Adcus 3mg/ml Solution for Infusion is essentially similar to Adenoscan which is approved in Ireland as well as in other countries in the EEA. Adcus 3mg/ml Solution for Infusion manufactured by Focus Pharmaceuticals is an intravenous solution for infusion with the same qualitative and quantitative composition in active substances as the reference product Adenoscan by Sanofi Aventis.

IV.2 Pharmacokinetics

Adenosine is impossible to study via classical absorption, distribution, metabolism and excretion (ADME) protocols. 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 <10 seconds. The *in vivo* half life may be even shorter.

The pharmacokinetics of adenosine has been adequately described in the clinical overview and is supported by appropriate literature references.

Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, the efficacy of the product should be unaffected by hepatic or renal insufficiency.

Biowaiver

A bioequivalence study is not necessary and this is in compliance with the guideline on the investigation of bioequivalence. (CPMP/EWP/QWP/1401/98 Rev. 1).

Article 10 of European Directive 2001/83/EEC, as amended, states that the applicant shall not be required to provide the results of clinical testing if it can be demonstrated that the product is a generic of a reference product, which has been authorised for not less than eight years in a member state, or in the community, provided that the product is intended for the same therapeutic use at the same dosage/route as the existing authorised product.

This application is based on the essential similarity of Adcus 3mg/ml Solution for Infusion to Adenoscan (Sanofi Aventis), which has been authorized and marketed in the EU for over 10 years.

Both the Focus Pharmaceuticals product, Adcus 3mg/ml Solution for Infusion, and Adenoscan (Sanofi Aventis), have the same qualitative and quantitative composition in terms of active substance, and are same pharmaceutical form, and hence no new clinical studies are presented.

In addition, Appendix II of CPMP/EWP/QWP/1401/98 Rev. 1/Corr states that:

“Bioequivalence studies are not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.”

Both the reference product and the Focus Pharmaceuticals product are aqueous solutions intended to be administered intravenously, containing the same active substance as the currently approved product. No bioequivalence studies have therefore been performed. A bioequivalence waiver is also included in the Clinical Overview (Module 2.5).

IV.3 Pharmacodynamics

Adenosine is an 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_1 and A_2 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_2 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.

IV.4 Clinical efficacy

The clinical efficacy of this medicinal product has been well described in the clinical overview, and is supported by appropriate literature references.

IV.5 Clinical safety

The clinical safety of Adenosine is well established. The product has been authorised and marketed in the European Union since 1995.

The most common adverse events (i.e. reported very common >1/10) associated with Adenosine Infusion use are: Headache, Dyspnoea, Abdominal discomfort, flushing and chest pressure/pain, feeling of thoracic constriction/oppression.

The pharmacology of the compound leads to a number of absolute contraindications which are listed in the SmPC of the reference product as:

Adcus is contra-indicated in patients suffering from:

- Hypersensitivity to the active substance or to any of the excipients
- 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

The SmPC contains the following 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.

Safety and efficacy in paediatric patients have not been established. Therefore adenosine is not recommended for use in children until further data become available.

V OVERALL CONCLUSIONS

User consultation

The Applicant provided justification for not conducting reader testing.

Conclusion:

The benefit risk was deemed to be positive.

VI REVISION DATE

January 2013