IPAR

Public Assessment Report

Scientific discussion

Adenosine 3 mg/ml Solution for Injection (ADENOSINE)

IE/H/240/01/DC

Date: 11th January 2013

This module reflects the scientific discussion for the approval of Adenosine 3 mg/ml Solution for Injection. The procedure was finalised on 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 Adenosine 3mg/ml Solution for Injection from Marketing Authorisation Holder Focus Pharmaceuticals Ltd.

For the indication of rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff- Parkinson-White Syndrome).
Adenosine 3mg/ml Solution for Injection is indicated in adults.

Diagnostic Indications
Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although Adenosine 3mg/ml Solution for Injection will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity.

Sensitisation of intra-cavitary electrophysiological investigations.

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

The application was made under article 10(1) of Directive 2001/83/EC as amended, i.e.
Adenosine 3mg/ml Solution for Injection is a generic version of the already approved reference product Adenocor Solution for Injection by Sanofi Aventis which has been marketed in the EU for more than 6 years.
Date of authorisation in UK is 14/8/1991. Consequently, Adenosine can be considered as a well-established drug.

II QUALITY ASPECTS

II.1 Introduction

This application is for Adenosine 3 mg/ml Solution for Injection packaged in a colourless, transparent Ph Eur Type I glass vial containing 2ml 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.

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 a 5 year 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 rapid bolus injection for intravenous use only. It contains 3 mg per ml (6 mg per 2 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 2ml 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 Adenocor 3mg/ml Solution for Injection. 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 2ml 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.4 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 Aedenosine 3 mg/ml Solution for Injection.

III NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of adenosine are well known. The reference medicinal product for this application is Adenocor. 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 Adenocor is considered to be sufficient and appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since adenosine 3 mg/ml Solution for Injection 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

Adenosine 3mg/ml Solution for Injection is a generic version of the already approved reference product Adenocor by Sanofi Aventis which has been marketed in the EU for more than 10 years.
Date of authorisation in UK is 14/8/1991.

Consequently, 10 years have passed since the first approval of Adenosine in a member state of the European Union and reference can be made to preclinical and clinical documentation of the innovator.

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

Overall 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 Adenosine 3mg/ml Solution for Injection to Adenocor (Sanofi Aventis), which has been authorized and marketed in the EU for over 10 years.
Both the Focus Pharmaceuticals product, Adenosine 3mg/ml Solution for Injection, and Adenocor (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

Pharmacodynamic properties ATC Code: Other Cardiac Preparations C01EB 10

Adenosine is an 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 Adenosine 3mg/ml Solution for Injection (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.

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 1991.

The most common adverse events (i.e. reported very common >1/10) associated with adenosine Injection use are:
Cardiovascular disorders (bradycardia, sinus pause, atrioventricular block, atrial extrasystoles, skipped beats, ventricular extrasystoles, non-sustained ventricular tachycardia), dyspnoea, 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:

- Hypersensitivity to the active substance or to any of the excipients
- Sick sinus syndrome, second or third degree Atrio-Ventricular 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.

The SmPC contains the following precautions for use.

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.

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 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, Adenosine 3mg/ml Solution for Injection'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 Adenosine 3mg/ml Solution for Injection. It is therefore suggested that Adenosine 3mg/ml Solution for Injection should not be administered to patients receiving dipyridamole; if use of Adenosine 3mg/ml Solution for Injection is essential, dipyridamole should be stopped 24 hours before hand, or the dose of Adenosine 3mg/ml Solution for Injection should be greatly reduced*).*

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, Adenosine 3mg/ml Solution for Injection should be used with caution in patients with a prolonged QT interval, whether this is drug induced or of metabolic origin. Adenosine 3mg/ml Solution for Injection is contraindicated in patients with Long QT syndrome.

Adenosine may precipitate or aggravate bronchospasm.

Safety and efficacy in paediatric patients have not been established. No data are available. No controlled paediatric study has been undertaken. Published uncontrolled studies show similar effects of adenosine in adults and children: effective doses for children were between 0.0375 and 0.25mg/kg.

V OVERALL CONCLUSIONS

User consultation

The Applicant provided adequate justification for not conducting reader testing, this was accepted by all CMS.

Conclusion:

The benefit/risk was deemed to be positive and marketing authorisation was granted.

VI REVISION DATE

January 2013