Public Assessment Report
Decentralised Procedure

Adrenaline 1:1000 (1mg/mL) Solution for injection
(adrenaline tartrate)

Procedure No: UK/H/5988/001/DC

UK Licence No: PL 43946/0001

BRADEX S.A. Pharmaceutical Products
LAY SUMMARY

Adrenaline 1:1000 (1mg/mL) Solution for injection (adrenaline tartrate)

This is a summary of the Public Assessment Report (PAR) for Adrenaline 1:1000 (1mg/mL) Solution for injection (PL 43946/0001; UK/H/5988/001/DC). It explains how the application for Adrenaline 1:1000 (1mg/mL) Solution for injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Adrenaline 1:1000 (1mg/mL) Solution for injection.

For practical information about using Adrenaline 1:1000 (1mg/mL) Solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as Adrenaline Solution for injection in this lay summary.

What is Adrenaline Solution for injection and what is it used for?

Adrenaline solution for injection is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Adrenaline solution for injection is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Adrenaline solution for injection is used in lifethreatening emergencies such as severe allergic reactions or cardiac arrest.

How does Adrenaline Solution for injection work?

Adrenaline solution for injection contains the active substance adrenaline (as adrenaline tartrate), which belongs to a group of medicines called adrenergic and dopaminergic agents. Adrenaline is a natural antidote to chemicals released during an allergic reaction.

How is Adrenaline Solution for injection used?

Adrenaline solution for injection is available as a solution for injection. Adrenaline solution for injection is administered by a trained healthcare professional into a muscle (intramuscularly) or in to a bone (intraosseous). The product must be diluted before injection into a vein. Adrenaline injection should not be used in areas such as fingers, toes, ears, nose or penis, as the blood supply to these areas might become inadequate.

Adrenaline solution for injection can only be obtained with a prescription.

For further information on how Adrenaline Solution for injection is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Adrenaline Solution for injection have been shown in studies?

As adrenaline is a well-known substance and its use in the treatment of lifethreatening emergencies such as severe allergic reactions or cardiac arrest is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of adrenaline in the treatment of lifethreatening emergencies such as severe allergic reactions or cardiac arrest.
What are the possible side effects of Adrenaline Solution for injection?
Like all medicines Adrenaline solution for injection can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Adrenaline solution for injection, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet for Adrenaline solution for injection.

Why is Adrenaline Solution for injection approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Adrenaline solution for injection outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of Adrenaline Solution for injection?
A Risk Management Plan has been developed to ensure that Adrenaline solution for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Adrenaline solution for injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Adrenaline solution for injection
Germany, Hungary, Spain and the UK agreed to grant a Marketing Authorisation for Adrenaline solution for injection on 05 May 2016. A Marketing Authorisation was granted in the UK to BRADEX S.A. Pharmaceutical Products on 02 June 2016.

The full PAR for Adrenaline solution for injection, solution follows this summary.

For more information about treatment with Adrenaline solution for injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2016.
SCIENTIFIC DISCUSSION

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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Adrenaline 1:1000 (1mg/mL) Solution for injection (PL 43946/0001; UK/H/5988/001/DC) is approvable. The product is a prescription-only medicine (POM) and is indicated for:

- cardiopulmonary resuscitation
- acute anaphylaxis

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Hungary and Spain as Concerned Member States (CMS). The application for Adrenaline 1:1000 (1mg/mL) Solution for injection was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance (adrenaline) of well-established use. Adrenaline has been widely used in the EU for many years.

Adrenaline is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha- and beta-adrenergic receptors and its effects on target organs are therefore complex. It is used to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise-induced anaphylaxis.

Adrenaline has a strong vasoconstrictor action through alpha-adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacological features in anaphylactic shock.

Adrenaline stimulates bronchial beta-adrenergic receptors and has a powerful bronchodilator action. Adrenaline also alleviates pruritis, urticaria and angioedema associated with anaphylaxis.

No new original non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of good manufacturing practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The member states considered that the application could be approved at the end of procedure (Day 210) on 05 May 2016. After a subsequent National phase, the UK granted a Marketing Authorisation (PL 43946/0001) for this product on 02 June 2016.
II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10a of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is presented as a clear, colourless sterile solution.

Each ml of solution for injection contains 1 mg of adrenaline (epinephrine) as adrenaline tartrate, as active ingredient.

The other ingredients consist of sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) sodium metabisulfite (E223) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All of the excipients meet the requirements of the current European Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for these excipients.

The product is supplied in amber coloured type I glass ampoules. The pack sizes are 10, 25 and 50 ampoules in a box.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance

Adrenaline tartrate

International Non-proprietary Name (INN): Adrenaline tartrate
Chemical name: (1R)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)ethanol hydrogen (2R,3R)-2,3-dihydroxybutanedioate (Ph. Eur.)
Molecular formula: C_{9}H_{13}NO_{3} C_{4}H_{6}O_{6}
Molecular weight: 333.3 g/mol
Structural formula:

Description: White to greyish white or light brownish-grey, odourless, crystalline powder.

Solubility: Freely soluble in water (1 in 3), slightly soluble in 96% ethanol (1 in 520) and methanol, practically insoluble in chloroform, methane chloride and ether.

Adrenaline tartrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, adrenaline tartrate, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3 Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, anti-oxidant free solution for injection containing 1 mg/ml adrenaline (as adrenaline tartrate). Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. The test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months with the special storage conditions ‘Keep the ampoules in the outer carton in order to protect from light’ and ‘Store below 25°C’ has been accepted for the unopened product.

After dilution:
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and when diluted to 0.1 mg/mL in sodium chloride 0.9 % would normally not be longer than 24 hours at 2 to 8°C, 3 hours at 23-27°C when exposed to light, or 6 hours at 23 to 27°C when protected from light.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application.

II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of adrenaline are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacokinetics
The pharmacokinetic properties of adrenaline are well known and adequately described in the applicant’s non-clinical overview.

III.3 Pharmacodynamics
The pharmacodynamic properties of adrenaline are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of adrenaline are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). It is agreed that the risks to the environment are not expected to increase as the proposed product will be used to substitute other currently marketed forms of adrenaline.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for this application, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The legal basis of this application is a well-established medicinal use according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literatures.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

The toxicology, pharmacokinetic and pharmacodynamic properties, efficacy in specific indications and the safety profile of adrenaline are considered well established. However, there are limited data in various areas and gaps in the evidence so its use under certain conditions is based mainly on empirical data and expert consensus.

The initially submitted clinical overview included a large number of publications on the clinical pharmacology, efficacy and safety of adrenaline in the proposed indications. However, the papers were generally presented in an abstract format with limited critical discussion and justification for the actual claimed indications and no specific information was provided to support the recommended posology. The applicant has provided an updated Clinical Overview that resolved the issues.

IV.2 Pharmacokinetics
No new original clinical pharmacokinetic data have been submitted and none are required for an application of this type. The pharmacokinetic profile of adrenaline is well-known. Bibliographic pharmacokinetic data have been provided to support the application. An adequate summary of the pharmacokinetic profile of adrenaline has been provided.
IV.3 Pharmacodynamics
The clinical pharmacology of adrenaline is well-known. An adequate summary of the pharmacodynamic profile of adrenaline has been presented in the clinical overview.

IV.4 Clinical Efficacy
No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of adrenaline is well-established. Efficacy is adequately reviewed in the clinical overview.

Hypersensitivity reactions and anaphylactic shock
The use of adrenaline in acute anaphylaxis is well established and this indication has already been approved for several other similar adrenaline products.

With regard to the recommended posology, it accurately reflects the clinical guidelines such as: EAACI Food Allergy and Anaphylaxis Guidelines Group; the Working Group of the Resuscitation Council (UK) on the Emergency treatment of anaphylactic reactions, guidelines for healthcare providers; the European academy of allergology and clinical immunology (The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007); the European Resuscitation Council (ERC) Guidelines for Resuscitation.

Cardiopulmonary resuscitation
As with acute anaphylaxis, the role of adrenaline in cardiac arrest and resuscitation is well established.

With regard to recommended posology, the relevant guidelines were reviewed to ensure that the SmPC accurately reflects their recommendations: the European Resuscitation Council (ERC) Guidelines for Resuscitation for adults and children as well as the relevant UK Resuscitation Council guidelines on advanced life support.

Further to the above, use of the proposed specific formulation for intravenous use in the proposed indications was also considered.

During assessment of this application issues were raised in regard to adequacy of a 1:1000 adrenaline formulation for intravenous use in cardiopulmonary resuscitation and in the treatment of acute anaphylaxis. Following review of the data provided by the company, the clinical guidelines as well as recent relevant regulatory reviews it was concluded that, overall, given the intended use of this product i.e. only in medical emergencies its use for intravenous (IV) administration (if needed, after dilution to 1:10000 as appropriate) in both acute anaphylaxis and cardiopulmonary resuscitation could be acceptable.

Among others, the below two pieces of information were particularly considered:
1. Current clinical guidelines on cardiopulmonary resuscitation do not mention or recommend any specific adrenaline solution for IV administration for adults, and there are no warnings against the use of a 1:1000 formulation. These include:
   a. 2015 European Resuscitation Council Guidelines for Resuscitation
   b. 2015 Resuscitation Council UK, Adult advanced life support
   c. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care
2. The principle of diluting a 1:1000 solution to 1:10000 for IV use in case of medical emergency, if required, was accepted in the conclusions of the Paediatric work sharing (PdWS) for the epinephrine procedure number MT/W/009/pdWS/001 in conformity with Article 45 of the Paediatric regulation (EC) 1901/2006 as amended, when it was concluded, among others, that
   *The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department*
(ED) setting. Epinephrine injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine 1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used with extreme caution and is best reserved for specialists familiar with IV use of epinephrine (adrenaline).

Although the above mainly concerned the treatment of anaphylaxis, the possibility of diluting a 1:1000 formulation, if necessary, was considered an acceptable practice. It was further considered that this is also applicable to a more critical, life and death situation, such as during cardiopulmonary resuscitation, if required.

Based on the above, taking also into account the specific product characteristics and that this concerned a 1mg ampoule which makes further dilution, if needed, relatively straightforward with a lower risk of preparation and administration errors, it was concluded (following also internal consultations and discussions) that its use for IV administration in both acute anaphylaxis and cardiopulmonary resuscitation could be accepted.

Relevant safety information and warnings are included in the Summary of product Characteristics (SmPC).

**IV.5 Clinical Safety**

No new safety data were supplied or required for this bibliographic application. The safety profile of adrenaline is well-known and has been adequately summarised by the Applicant in the clinical overview.

The applicant has provided a review of safety data on adrenaline from various sources, which is consistent with its known effects. In general, the common adverse effects reflect the known primary pharmacology of adrenaline. The main risk is inappropriate dosing or route of administration in anaphylaxis. In patients with a spontaneous circulation, intravenous adrenaline of an inadequate solution can cause life-threatening hypertension, tachycardia, arrhythmias and myocardial ischaemia. Excessive infusion rates may also compromise blood flow to peripheral organs.

There are no absolute contraindications to treatment with adrenaline in any patient experiencing severe anaphylaxis or cardiac arrest, although the benefit risk is clearly different between the two situations, particularly with excessive or inappropriate use of adrenaline in patients with a spontaneous circulation. In anaphylaxis, the risk benefit includes a consideration of patients at particular risks from arrhythmias, hypertension or ischaemic heart disease, or patients taking monoamine oxidase inhibitors, or medications which may sensitize the myocardium to arrhythmias.

As would be expected, there is limited direct evidence for interactions specifically in the emergency settings of use proposed, a number of interactions are possible based either on pharmacokinetic considerations (e.g. MAO inhibitors) or pharmacodynamics (e.g. sympathomimetics, alpha or beta-blocking agents, antidepressants), however in life-threatening emergencies such as cardiac arrest or severe anaphylaxis these are not a contra-indication to adrenaline use.

The applicant has made changes to the safety information of the SmPC.
IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Adrenaline 1:1000 (1mg/mL) Solution for injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration error; lack of drug effect, tissue necrosis, peripheral ischemia</td>
<td>Labelling: Sections 4.4. and 4.8 of the SmPC list this safety concern. Other routine risk minimisation measures. This product is for emergency use only and medical supervision of the patients is necessary after administration. For hospital use only.</td>
<td>None</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Adrenaline 1:1000 (1mg/mL) Solution for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of adrenaline are well-known, no additional data were required.

EFFICACY

No new clinical data were submitted and none were required for this type of application.
The published literature supports the efficacy of the product in the proposed indication and posology. The efficacy of adrenaline is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY
The safety profile of adrenaline is well-known. The literature review identified no new or unexpected safety issues or concerns.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with adrenaline is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling is listed below:
Adrenaline 1mg/10ml (1:10,000) solution for injection in prefilled syringe
Adrenaline 1mg/10ml (1:10,000) solution for injection in prefilled syringe
## Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>