Public Assessment Report

Decentralised Procedure

Adrenaline 1 mg/10 ml (1:10,000), solution for injection in pre-filled syringe

(adrenaline tartrate)

Procedure No: UK/H/5688/001/DC

UK Licence No: PL 14434/0031

Laboratoire Aguettant
LAY SUMMARY

Adrenaline 1 mg/10 ml (1:10,000) solution for injection in pre-filled syringe
(adrenaline tartrate)

This is a summary of the Public Assessment Report (PAR) for Adrenaline 1 mg/10 ml (1:10,000) solution for injection in pre-filled syringe (PL 14434/0031; UK/H/5688/001/DC). It explains how the application for Adrenaline 1 mg/10 ml (1:10,000) solution for injection in pre-filled syringe 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 mg/10 ml (1:10,000) solution for injection in pre-filled syringe.

For practical information about using Adrenaline 1 mg/10 ml (1:10,000) solution for injection in pre-filled syringe, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Adrenaline solution for injection’ or ‘Adrenaline 1:10,000 solution’ in this report.

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 for treatment of:
- cardiac arrest (unexpected loss of heart function, breathing and consciousness);
- acute anaphylaxis in adults (serious shock or collapse produced by a severe allergic reaction).

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 in a pre-filled syringe. Each millilitre (ml) of solution for injection contains 0.1 mg of adrenaline (as adrenaline tartrate). Each 10 ml pre-filled syringe contains 1 mg adrenaline (as adrenaline tartrate). Adrenaline solution for injection is administered by a doctor, nurse or paramedic into a vein or a bone. They will decide on the correct dose to be administered to the patient and when and how this should be given.

In case of life threatening allergic reactions (acute anaphylaxis):
Adults will be given a dose of 0.05 mg (0.5 ml of Adrenaline 1:10,000 solution) repeated as necessary until the desired response is achieved.

In case of cardiac arrest:
Adults: 1 mg (10 ml of Adrenaline 1:10,000 solution) is given into a vein or into a bone every 3-5 minutes until the heart starts to work.

Children above 5 kg: 10 microgram/kg (0.1 ml/kg of Adrenaline 1:10,000 solution) are given into a vein or into a bone every 3-5 minutes until the heart starts to work.
This medicinal product is not suitable for delivering a dose of less than 0.5 ml and should therefore not be used in neonates and infants for which the body weight is less than 5 kg.

Please read the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

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

**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 cardiac arrest and acute anaphylaxis in adults is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of adrenaline in the treatment cardiac arrest and acute anaphylaxis in adults.

**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.

The following side effects have been reported:
- anxiety,
- dyspnoea (difficulty in breathing),
- nervousness,
- fear,
- sweating,
- palpitations (irregular or faster heart beat),
- tachycardia (increased heart rate),
- pallor,
- tremors,
- weakness,
- dizziness,
- headache,
- nausea,
- vomiting,
- coldness of the extremities,
- hallucinations,
- syncope,
- hyperglycaemia (high blood sugar levels),
- hypokalaemia (low potassium levels in the blood),
- metabolic acidosis (increased acidity in the blood),
- mydriasis (dilatation of the pupil).

**In high dosages or for patients sensitive to adrenaline, side effects are:**
- cardiac dysrhythmia (irregular heartbeats/cardiac arrest),
- hypertension (with risk of cerebral haemorrhage),
- vasoconstriction (narrowing of the blood vessels for example cutaneous, in the extremities or kidneys),
- acute angina attacks,
- risk of acute myocardial infarction.

Repeated local injections may produce necrosis (tissue damage) at the site of injection as a result of vascular constriction (blood vessel constriction).

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 Adrenaline solution for injection.

**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**
Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Sweden and the UK agreed to grant a Marketing Authorisation for Adrenaline solution for injection on 23 November 2015. A Marketing Authorisation was granted in the UK to Laboratoire Aguettant on 10 December 2015.

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 February 2016.
SCIENTIFIC DISCUSSION

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Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Adrenaline 1 mg/10 ml (1:10,000) solution for injection in pre-filled syringe (PL 14434/0031; UK/H/5688/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for:

- cardiopulmonary resuscitation
- acute anaphylaxis in adults

The product may be referred to as ‘Adrenaline solution for injection’ in the rest of this report.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania and Sweden as Concerned Member States (CMS). The application for Adrenaline 1 mg/10 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.

The active substance, adrenaline, is a potent sympathomimetic agent, acting on both α- (α1 and α2) and β- (β1 and β2) adrenergic receptors.

No new 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 RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 23 November 2015. After a subsequent national phase, a licence was granted in the UK on 10 December 2015.

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 and colourless solution in a 10 ml pre-filled syringe.

Each ml of solution for injection contains 0.1 mg of adrenaline (as adrenaline tartrate). Each 10 ml pre-filled syringe contains 1 mg adrenaline (as adrenaline tartrate).
The other ingredients consist of sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

The product is supplied in 10 ml polypropylene pre-filled syringes without a needles, each individually packaged in a transparent blister and overwrapped in an aluminium pouch containing an oxygen absorbing sachet. The product is available in pack sizes of 1 or 10 pre-filled syringes in a box.

Not all pack sizes may be marketed.

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}

Mr: 333.3

Structural formula:

![Structural formula of Adrenaline tartrate]

Description: White to greyish white crystalline

Solubility: Freely soluble in water, slightly soluble in ethanol (96 per cent)

Isomerism: Adrenaline tartrate shows optical activity.

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 (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/10 ml adrenaline (as adrenaline tartrate) packaged in 10 ml pre-filled syringes. Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.
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. 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 2 years with the special storage conditions, ‘Do not freeze. Store in the aluminium pouch in order to protect from light and oxygen.’ has been accepted for the unopened product.

After opening the pouch the product must be used immediately.

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.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
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 application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

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

IV.2 Pharmacokinetics
No new 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.

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. No new or unexpected safety issues arose from the submitted safety data.

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 solution for injection.

The MAH identified the following as safety concerns:

<table>
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<th>Summary of safety concerns</th>
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<td>Important identified risks</td>
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<tr>
<td>Important potential risks</td>
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<tr>
<td>Missing information</td>
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</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 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 safety 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.
### Annex 1 - 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 IB/II variations, PSURs, commitments)

<table>
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<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>
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<td>Y/N (version)</td>
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