Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Ephedrine Hydrochloride 30 mg/ml Solution for Injection

(ephedrine hydrochloride)

Procedure No: UK/H/6786/001/DC

UK Licence No: PL 01502/0103

Hameln Pharmaceuticals Ltd

LAY SUMMARY

Ephedrine Hydrochloride 30 mg/ml Solution for Injection

This is a summary of the Public Assessment Report (PAR) for Ephedrine Hydrochloride 30 mg/ml Solution for Injection (PL 01502/0103; UK/H/6786/001/DC). It explains how Ephedrine Hydrochloride 30 mg/ml Solution for Injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Ephedrine Hydrochloride 30 mg/ml Solution for Injection.

The product will be referred to as Ephedrine Injection throughout the remainder of this public assessment report (PAR).

For practical information about using Ephedrine Injection patients should read the package leaflet or contact their doctor or pharmacist.

What is Ephedrine Injection and what is it used for?
Ephedrine Injection is a 'generic medicine'. This means that Ephedrine Injection is similar to a 'reference medicine' already authorised in the European Union (EU) called Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd).

Ephedrine Injection is used to relieve low blood pressure during spinal or epidural anaesthesia. It raises blood pressure by temporarily reducing the blood supply to small blood vessels.

How does Ephedrine Injection work?
Ephedrine Injection contains the active ingredient ephedrine. Ephedrine belongs to a group of medicines called sympathomimetics. Sympathomimetic drugs affect the part of your nervous system that works automatically.

How is Ephedrine Injection used?
The pharmaceutical form of this medicine is a solution for injection. The route of administration of this medicine is via syringe into a vein (intravenous). Ephedrine Injection will be given to the patient by their doctor.

The patient's doctor will decide what dose to give and how and when the injection will be given.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Ephedrine Injection have been shown in studies?
No additional clinical studies were needed as Ephedrine Injection is a generic medicine that is an aqueous solution that is given by injection and contains the same active as the reference medicine Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd).

What are the possible side effects of Ephedrine Injection
Because Ephedrine Injection is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Ephedrine Injection, see section 4 of the package leaflet available on the MHRA website.

Why was Ephedrine Injection approved?
It was concluded that, in accordance with EU requirements, Ephedrine Injection has been shown to be comparable to Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd). Therefore, the MHRA decided that, as for Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ephedrine Injection?
A risk management plan (RMP) has been developed to ensure that Ephedrine 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 Ephedrine 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 Ephedrine Injection
Germany and the UK agreed to grant a Marketing Authorisation for Ephedrine Injection on 05 June 2018. A Marketing Authorisation was granted in the UK on 08 June 2018.

The full PAR for Ephedrine Injection follows this summary.

For more information about treatment with Ephedrine Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2018.

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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 Ephedrine Injection (PL 01502/0103; UK/H/6786/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the reversal of hypotension from spinal or epidural anaesthesia.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany as a Concerned Member State (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection which was first granted to Macarthys Laboratories Ltd on 21 May 1990.

Ephedrine is a sympathomimetic amine which stimulates both α- and β-adrenergic receptors. Ephedrine is chemically an alkaloid and exhibits optical isomerism. This isomer is 1R, 2S-ephedrine. It works mainly by increasing the activity of norepinephrine on adrenergic receptors and also releases noradrenaline from storage sites. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle and decreases uterine activity. Ephedrine also has central nervous system stimulant effects.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. Since this application concerns a generic version of ephedrine hydrochloride, with essential similarity to the reference product, Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd), intended for parenteral use, a bioequivalence study is not required (Appendix II of CPMP/EWP/QWP/1401/98 Rev 1).

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 manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 05 June 2018. After a subsequent national phase, a licence was granted in the UK on 8 June 2018.

II QUALITY ASPECTS

II.1 Introduction

Each ml of solution contains 30 mg of ephedrine hydrochloride. The only excipient is water for injections.

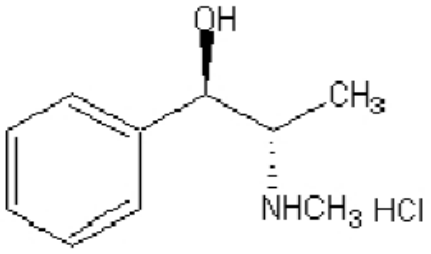
The finished product is supplied in 1 ml colourless glass one-point-cut (OPC) ampoules, type I containing 1 ml solution for injection. Packed into cartons of 5 or 10 ampoules.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance

INN: Ephedrine hydrochloride
Chemical name: (1R,2S)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride
Structural formula:



Molecular formula: $C_{10}H_{16}ClNO$
Molecular weight: 201.7
Characters: White or almost white, crystalline powder or colourless crystals.

Ephedrine hydrochloride is the subject of a European Pharmacopeia monograph.

All aspects of the manufacture and control of the active substance, ephedrine hydrochloride, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious solution for injection/infusion containing 30 mg of ephedrine hydrochloride per each ml of solution that is comparable to the originator product Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd).

A satisfactory account of the pharmaceutical development has been provided.
The excipient complies with its respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for the excipient. Suitable batch analysis data have been provided for the excipient.

This product contains no materials of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specifications have been provided. 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. The data from these studies support a shelf-life of 2 years for the unopened vial with the storage condition 'Keep the container in the outer carton in order to protect from light'.

In-use shelf life:

Chemical and physical in-use stability has been demonstrated for 72 hours at 25°C.

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 would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ephedrine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant's non-clinical expert report 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 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ephedrine 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.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

According to the regulatory requirements of CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of ephedrine hydrochloride.

Based on the data provided, Ephedrine Hydrochloride 30 mg/ml Solution for Injection can be considered a generic of Ephedrine Hydrochloride 30 mg per 1 ml Solution for Injection (Macarthys Laboratories Ltd).

IV.2 Pharmacokinetics

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as a parenteral aqueous solution containing the same qualitative and quantitative composition in terms of active substance and excipients and is of the same pharmaceutical form as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for an application of this type.

IV.6 Risk Management Plan (RMP)

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Adrenaline (Epinephrine) Injection 1 in 1000. The bridging report submitted by the applicant has been found acceptable.

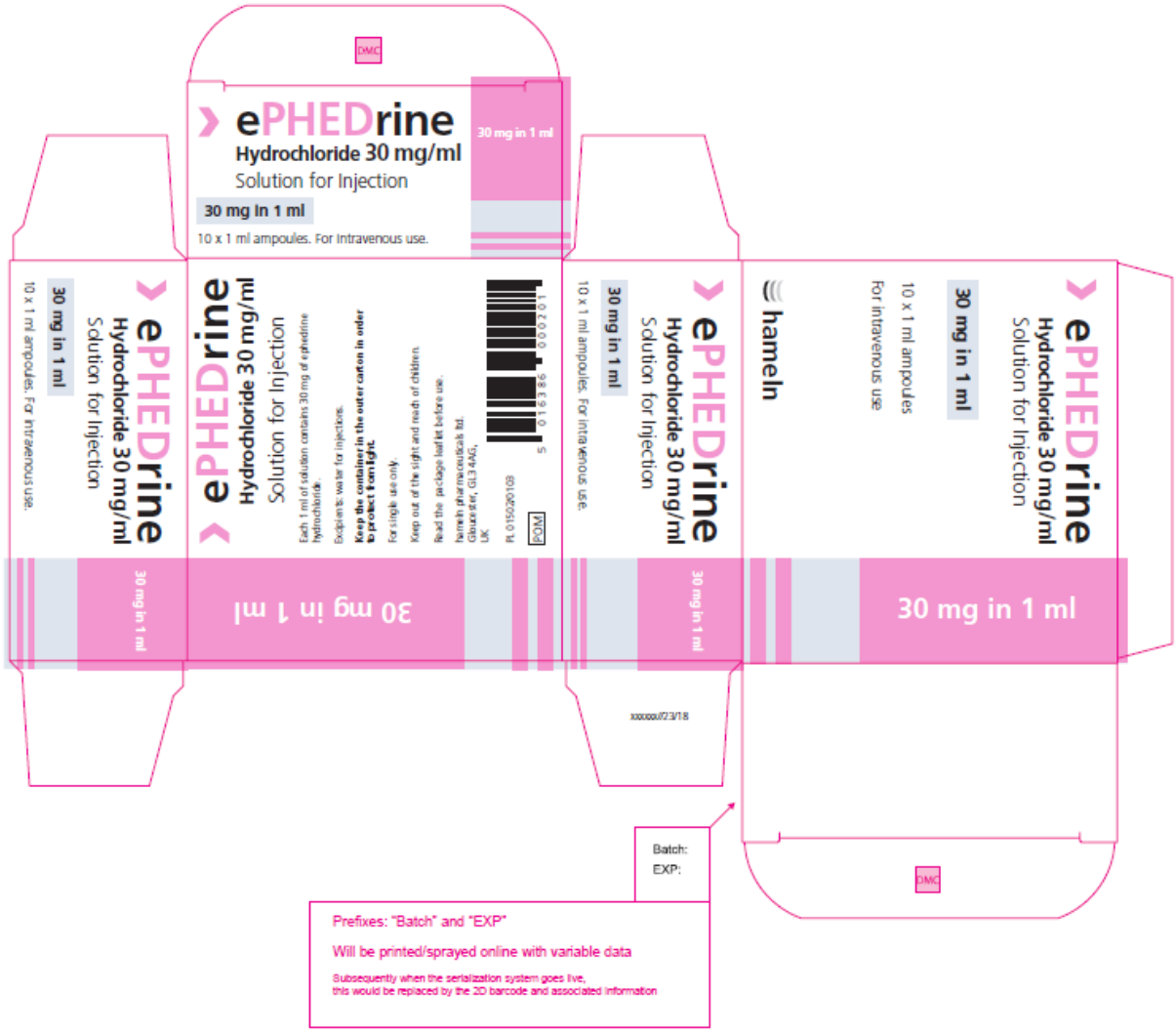
VI Overall conclusion, benefit/risk assessment and recommendation

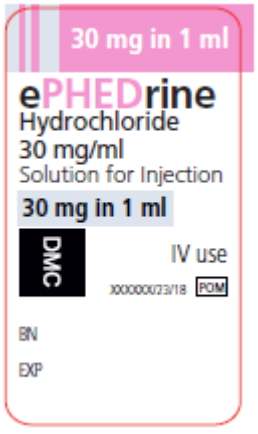
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ephedrine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:





Annex 1

Table of content of the PAR update

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

Date submitted	Application type	Scope	Outcome