Metaraminol 10mg/ml Solution for Injection or Infusion

(metaraminol tartrate)

PL 13079/0011

UKPAR

South Devon Healthcare NHS Foundation Trust
LAY SUMMARY

Metaraminol 10mg/mL Solution for Injection or Infusion
(metaraminol tartrate)

This is a summary of the Public Assessment Report (PAR) for Metaraminol 10mg/mL Solution for Injection or Infusion (PL 13079/0011). It explains how the application for Metaraminol 10mg/mL Solution for Injection or Infusion 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 Metaraminol 10mg/mL Solution for Injection or Infusion.

The product may be referred to as ‘Metaraminol injection’ in this report.

For practical information about using Metaraminol injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metaraminol injection and what is it used for?
Metaraminol injection is a ‘generic’ medicine’. This means that Metaraminol injection is similar to a ‘reference medicine’ already authorised in the UK called Aramine 10mg/ml solution for injection (PL 00025/5020R; Merck, Sharp & Dohme Limited), which was granted a full Marketing Authorisation on 14 June 1989. Aramine 10mg/ml solution for injection (PL 00025/5020R; Merck, Sharp & Dohme Limited) was originally granted a Product Licence of Right on 26 February 1973.

Metaraminol injection is used to raise low blood pressure to normal levels in an emergency situation.

How does Metaraminol injection work?
This medicine contains metaraminol (as metaraminol tartrate), which belongs to a group of medicines called vasopressors which work by narrowing the blood vessels causing blood pressure to rise.

How is Metaraminol injection used?
Metaraminol injection is available as a solution for injection/infusion. It is given by a doctor or nurse into a vein by injection/infusion.

The doctor will decide the correct dosage and how and when the injection will be given.

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

Metaraminol injection can only be obtained on prescription and is for use only in hospitals.

What benefits of Metaraminol injection have been shown in studies?
No additional studies were needed as Metaraminol 10mg/mL Solution for Injection or Infusion is a generic medicine that is given by infusion or injection and contains the same active substance as the reference medicine Aramine 10mg/ml solution for injection (PL 00025/5020R; Merck, Sharp & Dohme Limited).
What are the possible side effects from Metaraminol?
Like all medicines, Metaraminol injection can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Metaraminol injection, see section 4 of the package leaflet or the Summary of Product Characteristics available on the MHRA website.

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

Why is Metaraminol injection approved?
The MHRA decided that the benefits outweigh the identified risks and recommended that Metaraminol injection can be approved for use.

What measures are being taken to ensure the safe and effective use of Metaraminol?
A Risk Management Plan has been developed to ensure that Metaraminol 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 Metaraminol 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 Metaraminol injection.
A Marketing Authorisation was granted in the UK on 06 July 2015.

The full PAR for Metaraminol injection follows this summary.

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

This summary was last updated in August 2015.
Metaraminol 10mg/ml Solution for Injection or Infusion
(metaraminol tartrate)

PL 13079/0011

SCIENTIFIC DISCUSSION

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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted South Devon Healthcare NHS Foundation Trust a Marketing Authorisation for the medicinal product Metaraminol 10mg/mL Solution for Injection or Infusion (PL 13079/0011) on 06 July 2015. The product is a prescription--only medicine (POM) and is indicated for the treatment of acute hypotension due to loss of vasoconstrictor tone as may occur during spinal anaesthesia and as an adjunct to accepted remedial procedures.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator product Aramine 10mg/ml solution for injection (PL 00025/5020R), which was granted a full Marketing Authorisation on 14 June 1989. Aramine 10mg/ml solution for injection (PL 00025/5020R; Merck, Sharp & Dohme Limited), was originally granted a Product Licence of Right on 26 February 1973.

The product licence for Aramine 10mg/ml solution for injection was cancelled on the 02 of April 2009 and is not marketed in the UK or in the European Union.

Metaraminol 10mg/mL Solution for Injection or Infusion contains the active ingredient metaraminol (as metaraminol tartrate), which is a sympathomimetic agent, which falls into the adrenergic and dopaminergic pharmacotherapeutic group. Metaraminol is taken up by adrenergic neurones in a similar way to noradrenaline. This uptake is inhibited by noradrenaline itself, cocaine and ouabain. It acts as an alpha, receptor agonist in peripheral vessels, stimulating the release of noradrenaline and to a lesser extent adrenaline, and also acts directly on the beta, receptors in the myocardium.

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

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for an aqueous parenteral product, containing the same active substance as the reference product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Metaraminol 10mg/mL Solution for Injection or Infusion outweigh the risks and a Marketing Authorisation was granted.

II  QUALITY ASPECTS

II.1  Introduction

The application is submitted in accordance with Article 10(1) 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.

Each 1 mL of solution for injection for infusion contains 10mg of metaraminol (as tartrate). The other ingredients consist of sodium chloride, sodium metabisulfite (E223) and water for injections.

The finished product is supplied in glass ampoules containing 1mL of a clear solution for injection or infusion, in a pack size of 10 ampoules packaged in cartons.
Satisfactory specifications and Certificates of Analysis have been provided for the primary packaging components. All primary packaging comply with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

Metaraminol tartrate

INN: Metaraminol tartrate
Chemical name: (IR, 2S)-2-amino-l-(3-hydroxyphenyl)propan-l-ol hydrogen (2R,3R)-tartrate
Structure:

![Chemical Structure of Metaraminol Tartrate]

Molecular formula: C_{9}H_{13}NO_{2}·C_{4}H_{6}O_{6}
Mr: 317.3
Appearance: A white crystalline powder.
Solubility: Freely soluble in water, sparingly soluble in ethanol (96%) and practically insoluble in ether.

Metaraminol tartrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests 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. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3 Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, solution containing 10 mg/ml of metaraminol (as metaraminol tartrate) that could be considered a generic medicinal product of the reference product Aramine 10mg/ml solution for injection (PL 00025/5020R; Merck, Sharp & Dohme). Suitable pharmaceutical development data have been provided.

All the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for this excipient showing compliance with the proposed specification.

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 specification. 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 for the unopened has been approved, with the special storage conditions ‘Do not store above 25ºC.’

After dilution, chemical and physical in-use stability has been demonstrated for 48 hours when the diluted product is stored between 2 to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 48 hours at 2 to 8°C unless opening has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application for Metaraminol 10mg/mL Solution for Injection or Infusion.

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.

III NON-CLINICAL ASPECTS
III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of metaraminol 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 this type of application.

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 Pharmacodynamics

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

III.3 Pharmacokinetics

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

III.4 Toxicology

The toxicological properties of metaraminol 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). As the application is for generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Metaraminol 10mg/mL Solution for Injection or Infusion, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of metaraminol is well-known. No new clinical pharmacokinetic data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for an aqueous parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions containing the same active substance as the currently approved product (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

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

IV.2 Pharmacokinetics

The pharmacokinetic properties of metaraminol are well known and are adequately described in the applicant’s non-clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of metaraminol are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

**IV.4 Clinical Efficacy**
No new efficacy data have been submitted and none are required for this application for a parenteral product. The clinical efficacy of metaraminol is well-known. Efficacy is adequately reviewed in the clinical overview.

**IV.5 Clinical Safety**
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

**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 Metaraminol 10mg/mL Solution for Injection or Infusion.

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
</tr>
<tr>
<td>Overdosage</td>
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<tr>
<td>Perpetuation of shock due to local vasoconstriction</td>
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<tr>
<td>Use in patients with cirrhosis</td>
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<tr>
<td>Excessively rapid blood pressure changes</td>
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<tr>
<td>Use in patients with malaria</td>
</tr>
<tr>
<td>Interactions: Cyclopropane, Halothane, Monoamine oxidase inhibitors, Alpha-adrenoceptor blocking agents, Digitalis</td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<tr>
<td>Use in the elderly</td>
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<tr>
<td>Use in children</td>
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<tr>
<td>Use in pregnancy</td>
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<tr>
<td>Use in breastfeeding</td>
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<tr>
<td>Extravasation</td>
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<tr>
<td>Skin irritation following spillage</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

**IV.7 Discussion of the clinical aspects**
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, as amended. 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 Metaraminol 10mg/mL Solution for Injection or Infusion 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 are well-known.

EFFICACY
No new clinical data were submitted and none were required for this type of application.

SAFETY
The safety profile of metaraminol is well-known. No new or unexpected safety issues or concerns arose from this application.

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 metaraminol 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.

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:
Steps taken after the initial procedure with an influence on the Public Assessment Report

<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IB variation to update sections 2, 4.2, 4.8 and 6.2 of the SmPC.</td>
<td>PL 13079/0011 - 0010</td>
<td>SmPC</td>
<td>01/07/2016</td>
<td>20/07/2016</td>
<td>Approval</td>
<td>Y (Annex 1)</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 13079/0011 - 0010
Product: Metaraminol 10mg/ml Solution for Injection or Infusion
Marketing Authorisation Holder: South Devon Healthcare NHS Foundation Trust
Active Ingredient(s): Metaraminol tartrate

Reason:
Type IB variation to update sections 2, 4.2, 4.8 and 6.2 of the SmPC.

Section 2 has been updated as the unit of the amount of sodium in 1mL of the product is incorrect. The wording has been changed from “Each 1 mL of solution contains 98.4 mmol (2.26 mg) sodium” to “Each 1 mL of solution contains 98.3 micromol (2.26 mg) sodium”.

Section 4.2, 4.8 and 6.2 have been updated to correct minor typographical errors.

Supporting Evidence
Revised SmPC fragments 2, 4.2, 4.8 and 6.2 have been provided.

The calculation to support the correct unit for the amount of sodium in 1mL in Section 2 of SmPC has been provided.

Evaluation
The amended sections of the SmPC and calculation to support the change in Section 2 are satisfactory.

The current SmPC is available on the MHRA website.

Decision
Approved on 20 July 2016.