Public Assessment Report

Decentralised Procedure

CHLORPHENAMINE 10 MG/ML SOLUTION FOR INJECTION

(chlorphenamine maleate)

Procedure No: UK/H/6020/001/DC

UK Licence No: PL 29831/0585

Wockhardt UK Limited
LAY SUMMARY
Chlorphenamine 10 mg/ml Solution for injection (chlorphenamine maleate)

This is a summary of the Public Assessment Report (PAR) for Chlorphenamine 10 mg/ml Solution for injection (PL 29831/0585; UK/H/6020/001/DC). It explains how the application for Chlorphenamine 10 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 Chlorphenamine 10 mg/ml Solution for injection.

For practical information about using Chlorphenamine 10 mg/ml Solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Chlorphenamine 10 mg/ml Solution for injection and what is it used for?
Chlorphenamine 10 mg/ml Solution for injection is a ‘generic medicine’. This means Chlorphenamine 10 mg/ml Solution for injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Chlorphenamine 10mg/ml Solution for injection (PL 12406/0013).

Chlorphenamine 10 mg/ml Solution for injection is used to relieve some of the main symptoms of a severe allergic reaction.

How does Chlorphenamine 10 mg/ml Solution for injection work?
This medicine contains the active substance chlorphenamine maleate, which is an anti-histamine. Anti-histamines work by inhibiting the release of histamine into the body that occurs during an allergic reaction.

How is Chlorphenamine 10 mg/ml Solution for injection used?
This medicine can only be obtained with a prescription.

The injection is usually given to the patient by a doctor or someone else trained in its administration. The injection is given beneath the skin, or into a muscle, or directly into a vein.

In adults, the usual dose is 10 mg to 20 mg (1 or 2 ampoules) up to a maximum of 40 mg (4 ampoules) in a 24 hour period. In children and adolescents the dose will be calculated according to the child’s age or body weight, as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>1 month to 1 year</td>
<td>0.25mg/kg</td>
</tr>
<tr>
<td>1 to 5 years</td>
<td>2.5mg to 5mg</td>
</tr>
<tr>
<td></td>
<td>OR 0.20mg/kg</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>5mg to 10mg</td>
</tr>
<tr>
<td></td>
<td>OR 0.20mg/kg</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>10mg to 20mg</td>
</tr>
<tr>
<td></td>
<td>OR 0.20mg/kg</td>
</tr>
</tbody>
</table>

The doctor may dilute chlorphenamine with sodium chloride 0.9% to make it easier to measure and inject the small amounts required for children.
When administered into a vein, the injection should be given slowly over a period of one minute to avoid a fall in blood pressure or central nervous system stimulation.

**What benefits of Chlorphenamine 10 mg/ml Solution for injection have been shown in studies?**
The company provided data from the published literature on chlorphenamine maleate. No additional studies were needed as Chlorphenamine 10 mg/ml Solution for injection is a generic medicine that is given as an injection and contains the same active substance, in the same concentration, as the reference medicine, Chlorphenamine 10 mg/ml Solution for injection (PL 12406/0013).

**What are the possible side effects of Chlorphenamine 10 mg/ml Solution for injection?**
Because Chlorphenamine 10 mg/ml Solution for injection is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Chlorphenamine 10 mg/ml Solution for injection, see section 4 of the package leaflet.

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

**Why was Chlorphenamine 10 mg/ml Solution for injection approved?**
It was concluded that, in accordance with EU requirements, Chlorphenamine 10 mg/ml Solution for injection has been shown to have comparable quality and to be comparable to Chlorphenamine 10 mg/ml Solution for injection (PL 12406/0013). Therefore, the MHRA decided that, as for Chlorphenamine 10 mg/ml Solution for injection (PL 12406/0013), the benefits outweigh the identified risks and recommended that Chlorphenamine 10 mg/ml Solution for injection can be approved for use.

**What measures are being taken to ensure the safe and effective use of Chlorphenamine 10 mg/ml Solution for injection?**
A risk management plan (RMP) has been developed to ensure that Chlorphenamine 10 mg/ml Solution for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Chlorphenamine 10 mg/ml 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 and reviewed continuously.

**Other information about Chlorphenamine 10 mg/ml Solution for injection**
Malta and the UK agreed to grant Marketing Authorisations for Chlorphenamine 10 mg/ml Solution for injection on 18 January 2016. A Marketing Authorisation was granted in the UK on 28 January 2016.

The full PAR for Chlorphenamine 10 mg/ml Solution for injection follows this summary. For more information about treatment with Chlorphenamine 10 mg/ml Solution for injection read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 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 Chlorphenamine 10 mg/ml Solution for injection (PL 29831/0585; UK/H/6020/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS).

This product is a Prescription Only Medicine (legal classification POM).

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The originator product is Chlorphenamine 10mg/ml Solution for Injection (PL 12406/0013; Archimedes Pharma UK Limited), which was granted a licence in the UK on 23 February 1998. This followed a change of ownership from Piriton Injection (PL 00036/0087; Stafford-Miller Limited) which was granted a licence in the UK on 14 February 1997. This, in turn, followed a change of ownership from PL 10949/0105; Glaxo welcome UK Limited), which was granted a licence in the UK on 15 October 1993.

Chlorphenamine 10 mg/ml Solution for injection is indicated for acute urticaria, control of allergic reactions to insect bites and stings, angioneurotic oedema, drug and serum reactions, desensitisation reactions, hayfever, vasomotor rhinitis and severe pruritus of non-specific origin.

This product contains the active ingredient chlorphenamine maleate, which is an anti-histamine. Antihistamines act by competing with histamine for H1-receptor sites on cells and tissues.

Chlorphenamine also has anticholinergic activity. The mechanism by which chlorphenamine exerts its anti-emetic, anti-motion sickness and anti-vertigo effects is not precisely known but may be related to its central actions. Further, most antihistamines, including chlorphenamine, cross the blood-brain barrier and probably produce sedation largely by occupying H1-receptors in the brain.

No new clinical or 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.

Chlorphenamine 10 mg/ml Solution for injection is an aqueous solution at the time of administration and in line with the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 18 January 2016. After a subsequent national phase, a licence was granted in the UK on 28 January 2016.
II QUALITY ASPECTS

II.1 Introduction
Chlorphenamine 10mg/ml Solution for injection is a clear, colourless sterile solution for injection. The pH of the solution is 4.0 – 5.2 and the osmolality is 261 – 319 mOsm/Kg. Each 1 ml of Chlorphenamine 10mg/ml Solution for injection contains 10mg of the active ingredient chlorphenamine maleate.

Other ingredients consist of the pharmaceutical excipients, namely sodium chloride and water for injections.

The finished product is packaged in 1ml clear, neutral glass (Type I, PhEur) ampoules. It is supplied in boxes of 5 ampoules.

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
rINN: Chlorphenamine maleate
Chemical name(s): (3RS)-3-(4-Chlorophenyl)-N,N-dimethyl-3-(pyridin-2-yl)propan-1-amine hydrogen (Z)-butenedioate

Structure:

Molecular formula: C_{16}H_{19}ClN_{2}C_{4}H_{4}O_{4}
Molecular weight: 390.9
Appearance: White or almost white crystalline powder
Solubility: Freely soluble in water, soluble in ethanol (96 %)

All aspects of the manufacture and control of the active substance chlorphenamine maleate from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated to support 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 globally acceptable and stable product that could be considered a generic medicinal product of the currently licensed product, Chlorphenamine 10mg/ml Solution for Injection (PL 12406/0013; Archimedes Pharma UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.
Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on two production scale batches of finished product. The results are satisfactory. The Applicant has committed to carry out process validation on a third production scale batch and the first two commercial batches.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. 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
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 30 months for the unopened ampoule, with no special storage conditions. The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

After dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 5°C in polypropylene syringes. 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Chlorphenamine 10mg/ml Solution for injection.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels 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 approved labelling is shown below:
III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of chlorphenamine maleate are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to chlorphenamine maleate is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Chlorphenamine 10mg/ml Solution for injection.

IV. CLINICAL ASPECTS
IV.1 Introduction
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 chlorphenamine maleate. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
A bioequivalence study was not submitted as the product meets the criteria regarding parenteral solutions specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous solution at the time of administration and contains an active substance in the same concentration as the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for
pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, 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 Chlorphenamine 10mg/ml Solution for injection.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| Hypersensitivity to the active substance, antihistamines or to any of the excipients | • Contraindication in SmPC section 4.3.  
• Listed in SmPC section 4.8.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use of monoamine oxidase inhibitors (MAOIs) within the last 14 days | • Contraindication in SmPC section 4.3.  
• Interaction described in SmPC section 4.5.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use in patients with epilepsy                       | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use in patients with raised intra-ocular pressure including glaucoma | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use in patients with prostatic hypertrophy          | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use in patients with severe hypertension or cardiovascular disease | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained professional. | None                                  |
| Use in patients with bronchitis                     | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
| Use in patients with bronchiectasis and asthma      | • Warning and precaution in SmPC section 4.4.  
• Prescription-only medicine, to be administered by a trained healthcare professional. | None                                  |
<p>| Use in patients with hepatic disease                | • Warning and precaution in SmPC section 4.4. | None                                  |</p>
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in patients with thyrotoxicosis</td>
<td>• Warning and precaution in SmPC section 4.4.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Concurrent use of hypnotics, anxiolytics, phenytoin or alcohol</td>
<td>• Interactions described in SmPC section 4.5.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Administration errors in children (dose calculation, accurate dilution and correct storage)</td>
<td>• Dilution and dosing guidelines specified in SmPC section 4.2</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Use during lactation</td>
<td>• Information provided in SmPC section 4.6.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Use in children and the elderly</td>
<td>• Warning and precaution in SmPC section 4.4.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Undesirable events listed in SmPC section 4.8.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Use while driving</td>
<td>• Warning given in SmPC section 4.7.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>• Dosing guidelines specified in SmPC section 4.2.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Described in SmPC section 4.9.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
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<tr>
<td>Use during pregnancy</td>
<td>• Information provided in SmPC section 4.6.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Prescription-only medicine, to be administered by a trained healthcare professional.</td>
<td></td>
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</tbody>
</table>

**IV.7 Discussion of the clinical aspects**

It is recommended that a Marketing Authorisation is granted for Chlorphenamine 10mg/ml Solution for injection.
V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with chlorphenamine maleate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
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

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