Public Assessment Report

Decentralised Procedure

Cyclizine Lactate 50 mg/ml Solution for Injection

(Cyclizine lactate)

Procedure No: UK/H/6942/001/DC
UK Licence Number: PL 01883/0270

Macarthys Laboratories Limited (trading as Martindale Pharma).
LAY SUMMARY

Cyclizine Lactate 50 mg/ml Solution for Injection
(cyclizine lactate)

This is a summary of the Public Assessment Report (PAR) for Cyclizine Lactate 50 mg/ml Solution for Injection (PL 01883/0270; UK/H/6942/001/DC). It explains how Cyclizine Lactate 50 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 this product.

The product will be referred to as ‘Cyclizine Injection’ throughout the remainder of this PAR.

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

What is Cyclizine Injection and what is it used for?
Cyclizine Injection is a ‘generic medicine’. This means that Cyclizine Injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Valoid 50 mg/ml Injection/Cyclizine Lactate 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited). The reference product may be referred to as ‘Valoid 50 mg/ml Injection’ throughout the remainder of this report.

Cyclizine Injection may be used by adults. Cyclizine Injection may be used if the patient suffers from travel or motion sickness; nausea caused by cancer treatment (radiotherapy) or other medicines; or if the patient has had an operation, as general anaesthetics can sometimes cause sickness. Cyclizine Injection can also be used to treat sickness caused by some inner ear problems such as Meniere’s disease.

How does Cyclizine Injection work?
Cyclizine Injection contains the active ingredient cyclizine lactate which belongs to a group of medicines called antihistamines which can be used to help stop a patient feeling sick (nausea) or being sick (vomiting).

How is Cyclizine Injection used?
The pharmaceutical form of this medicine is a clear, colourless solution for injection and the route of administration is by slow injection into a vein (intravenously) or by injection into a muscle (intramuscularly).

The patient will be given Cyclizine Injection under supervision and their doctor will decide on a dose which is right for them.

The recommended dose for adults is:
- 50 mg up to three times a day.

For prevention of sickness after a normal operation:
The patient’s doctor will give the first dose of cyclizine by injection into a vein, approximately 20 minutes before the end of the operation.

The use of the injectable form of cyclizine has been associated with cases of transient paralysis following administration of the medicine. The onset of paralysis is usually within minutes of administration, affects the limbs, and fully resolves within hours of discontinuation of the medicine.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.
For further information on how Cyclizine Injection is used, refer to the package leaflet and the Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Cyclizine Injection have been shown in studies?**
No additional clinical studies were needed as Cyclizine Injection is a generic medicine that is given intravenously/intramuscularly as an aqueous solution and contains the same amount as the same active as the reference medicine Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited).

**What are the possible side effects of Cyclizine Injection?**
Because Cyclizine 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 Cyclizine Injection see section 4 of the package leaflet available on the MHRA website.

**Why was Cyclizine Injection approved?**
It was concluded that, in accordance with EU requirements, Cyclizine Injection has been shown to be comparable to Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited). Therefore, the MHRA decided that, as for Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited), the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Cyclizine Injection?**
A risk management plan (RMP) has been developed to ensure that Cyclizine Injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for Cyclizine 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 Cyclizine Injection**
Ireland and the UK agreed to grant a marketing authorisation for Cyclizine Injection on 07 January 2019.
Following a subsequent national phase, a Marketing Authorisation was granted in the UK on 23 January 2019.

The full PAR for Cyclizine Injection follows this summary.

This summary was last updated in February 2019.
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I INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Macarthys Laboratories Limited a Marketing Authorisation for the medicinal product Cyclizine Injection (PL 01883/0270; UK/H/6942/001/DC) on 23 January 2019. The product is a prescription only medicine (POM) indicated in adults for the prevention and treatment of nausea and vomiting including:
- Motion sickness when the oral route cannot be used.
- Nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period.
- Vomiting associated with radiotherapy especially for breast cancer since cyclizine does not elevate prolactin levels.
- Cyclizine injection, by the intravenous route, is also indicated pre-operatively in patients undergoing emergency surgery in order to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.

Cyclizine may be of value in relieving vomiting and attacks of vertigo associated with Menière’s disease and other forms of vestibular disturbance when the oral route cannot be used.

The application was submitted using the Decentralised procedure (DCP) with the UK as Reference Member State (RMS) and Ireland as 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 Valoid 50 mg/ml Injection which was first authorised to the marketing authorisation holder (MAH), The Wellcome Foundation Limited, in the UK on 12 August 1985 (PL 00003/5212R) and underwent a change of ownership procedure to the current MAH, Amdipharm UK Limited on 01 December 2003 (PL 20072/0010).

Cyclizine is a histamine H1 receptor antagonist of the piperazine class which is characterised by a low incidence of drowsiness. It possesses anticholinergic and antiemetic properties. The exact mechanism by which cyclizine can prevent or suppress both nausea and vomiting from various causes is unknown. Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre.

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 cyclizine, with essential similarity to the reference product, Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited), 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 are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

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 or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ 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 considered that the application could be approved at the end of procedure on 07 January 2018. After a subsequent national phase, a licence was granted in the UK on 23 January 2019.
II QUALITY ASPECTS

II.1 Introduction

Each 1 ml ampoule contains 50 mg cyclizine lactate as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactic acid and water for injections.

The finished product is packaged in 1ml Type I glass ampoules supplied in packs of 10 ampoules in an outer carton.

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: Cyclizine
Chemical name: 1-benzhydryl-4-methylpiperazine
Structure:

\[
\text{\begin{center}
\begin{tikzpicture}
\node (cyclizine) {\includegraphics[width=0.3\textwidth]{cyclizine_structure.png}};
\end{tikzpicture}
\end{center}
}\]

Molecular formula: \( \text{C}_{18}\text{H}_{22}\text{N}_{2} \)
Molecular weight: 266.38
Appearance: A white or creamy white, crystalline powder
Solubility: Practically insoluble in water. It dissolves in most organic solvents and in dilute acids

Cyclizine is the subject of an Active Substance Master File (ASMF).

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 for the active substance. 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 used.

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

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, clear, colourless solution for injection containing 50 mg cyclizine lactate per 1ml ampoule, that is a generic version of the reference product, Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia (Ph.Eur) monograph. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material 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 have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification
The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which 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 the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened ampoule with the storage conditions 'Store below 25ºC. Keep the ampoule in the outer carton in order to protect from light.'

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 cyclizine lactate 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.
Ill.4  Ecotoxicity/environmental risk assessment (ERA)
Since Cyclizine 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.

Ill.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
The safety and efficacy of cyclizine lactate are well known. As cyclizine lactate is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required.

The criteria for a generic application are outlined below:
1. The generic product has the same qualitative and quantitative composition in active substance as the reference product.
2. The generic product has the same pharmaceutical form as the reference medicinal product.
3. The generic product has demonstrated bioequivalence with the reference product, demonstrated by appropriate bioavailability studies*.

*According to the guideline CPMP/EWP/QWP/1401/98, bioequivalence studies are not required for this drug product because it will be administered as an aqueous parenteral solution containing the same active substance and the same excipients in similar amounts as the currently approved product.

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 cyclizine lactate.

Based on the data provided, Cyclizine Injection can be considered a generic of Valoid 50 mg/ml Injection (PL 20072/0010; Amdipharm UK Limited).

IV.2  Pharmacokinetics
Cyclizine Injection is indicated for parenteral use only. No bioequivalence studies are required for this type of product according to ‘Note for guidance on the investigation of bioavailability and bioequivalence’ (CPMP/EWP/QWP/1401/98) and the Applicant has submitted none. This is acceptable.

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

IV.4  Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5  Clinical safety
No new safety data were submitted and none are required.

IV.6  Risk Management Plan (RMP) and Pharmacovigilance System
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 Cyclizine Injection.

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.
IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation
The 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 PIL 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
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Cyclizine Injection is indicated for parenteral use only, therefore no bioequivalence studies are required for this type of product. Extensive clinical experience with cyclizine 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 (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
PAR Cyclizine Lactate 50 mg/ml Solution for Injection

Martindale Pharma
Cyclizine Lactate
50 mg/ml
Solution for Injection
For IV or IM use only
Intramuscularly or intravenously
PL 01883/0270 POM

Lot:
Exp.
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 II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
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