CYCLIZINE HYDROCHLORIDE 50 MG TABLETS

PL 20117/0216

UKPAR

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CYCLIZINE HYDROCHLORIDE 50 MG TABLETS

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LAY SUMMARY

On 3rd October 2012, the MHRA granted Morningside Healthcare Limited a Marketing Authorisation (licence) for Cyclizine Hydrochloride 50 mg Tablets.

Cyclizine Hydrochloride 50 mg Tablets contain the active ingredient, cyclizine hydrochloride, which belongs to a group of medicines called antihistamines.

Cyclizine Hydrochloride 50 mg Tablets can be used to help stop you feeling sick (nausea) or being sick (vomiting), including:

- travel or motion sickness
- nausea caused by cancer treatment (radiotherapy) or other medicines
- after an operation, as general anaesthetics can sometimes cause sickness
- vertigo (dizziness/giddiness) associated with middle ear problems, including Meniere's disease.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Cyclizine Hydrochloride 50 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

CYCLIZINE HYDROCHLORIDE 50 MG TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

On 3rd October 2012, the UK granted Morningside Healthcare Limited a Marketing Authorisation for the medicinal product Cyclizine Hydrochloride 50 mg Tablets (PL 20117/0216).

Cyclizine Hydrochloride 50 mg Tablets are available at pharmacies (P) and are indicated for the prevention and treatment of nausea and vomiting including:

• Motion sickness.
• 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 Tablets may be of value in relieving vomiting and attacks of vertigo associated with Meniere's disease and other forms of vestibular disturbance.

This application for Cyclizine Hydrochloride 50 mg Tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product to Valoid 50 mg Tablets, originally authorised to The Wellcome Foundation Limited on 29th August 1984 (PL 00003/5213R). This licence underwent changes of ownership to Paion UK Limited on 1st January 2001 (PL 18467/0001) and then to Amdipharm PLC on 1st December 2003 (PL 20072/0011).

Cyclizine is a histamine H_1 receptor antagonist of the piperazine class which is characterised by a low incidence of drowsiness. It possesses anticholinergic and antiemetic properties. It acts both on the emetic trigger zones and by damping the labyrinthine sensitivity.

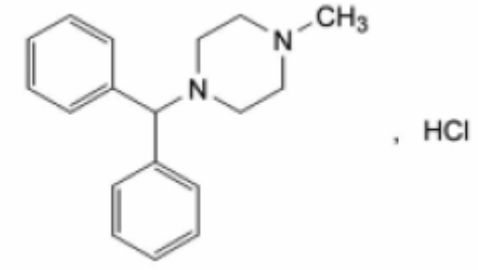
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Cyclizine hydrochloride

Chemical name: 1(Diphenylmethyl)-4-methyl piperazine hydrochloride

Structure:



Physical form: White to almost white crystalline powder

Molecular formula: $C_{18}H_{23}ClN_2.HCl$
Molecular weight: 302.8

The cyclizine hydrochloride used in the product complies with the European Pharmacopoeia monograph for cyclizine hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the drug substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations.

Stability studies have been performed with the drug substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.

DRUG PRODUCT

Other ingredients

Other ingredients in the tablet are the pharmaceutical excipients lactose monohydrate, maize starch, sodium starch glycolate, povidone, colloidal anhydrous silica and magnesium stearate.

All the ingredients comply with their relevant European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. A declaration has been provided that states that the milk used in the production of the lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. The magnesium stearate used in this product is of vegetable origin.

Pharmaceutical Development

The objective of the development programme was to produce a safe, efficacious product containing cyclizine hydrochloride that could be considered a generic medicinal product of Valoid 50 mg Tablets.

The applicant has provided suitable product development information. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution profiles were provided for the proposed and reference product.

Manufacturing Process

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 and has shown satisfactory results. Process validation data on commercial-scale batches have been provided and are satisfactory. A commitment to perform process validation on future commercial-scale batches has been provided.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

The product is packaged in blisters composed of polyvinyl chloride (PVC) and aluminium. The product comes in pack sizes of 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions ‘Keep the blisters in the outer carton in order to protect from light’. This is satisfactory.

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

The SmPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

The MAA form is pharmaceutically satisfactory.

Quality Overall Summary

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

From a quality point of view, it is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

To support the application, a single bioequivalence study has been provided:

A randomised, open-label, two-sequence, two-treatment, two-period, crossover, single-dose bioequivalence study comparing the pharmacokinetics of the test product Cyclizine Hydrochloride 50 mg Tablets versus the reference product Valoid (cyclizine hydrochloride) 50 mg Tablets (Amdipharm PLC) in healthy volunteers under fasted conditions.

Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. There was a washout period of 10 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values:

Pharmacokinetic parameters of cyclizine hydrochloride (Geometric Least Mean Squares and 90% Confidence Interval)

Treatment	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	C_{max} (ng/mL)
Test	388.43	447.87	18.87
Reference	381.51	436.79	18.53
Ratio (90% CI)	101.81 94.86 – 109.28	102.54 95.92 – 109.60	101.81 94.04 – 110.24

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for cyclizine hydrochloride lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference product.

Efficacy

This is a generic application based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

Safety

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this generic application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

The Pharmacovigilance System and the Risk Management Plan

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH 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.

A satisfactory justification for the absence of a Risk Management Plan has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product.

MAA Form
The MAA form is clinically satisfactory.

Clinical Overview
The clinical overview has been written by a suitably qualified person and is satisfactory.

Conclusion
The bioequivalence study has shown that Cyclizine Hydrochloride 50 mg Tablets can be considered as a generic medicinal product to the reference product Valoid 50 mg Tablets.

From a clinical point of view, it is recommended that a Marketing Authorisation is granted for this application.

OVERALL CONCLUSIONS AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Cyclizine Hydrochloride 50 mg Tablets 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.

CLINICAL

Bioequivalence has been demonstrated between the applicant's Cyclizine Hydrochloride 50 mg Tablets and the reference product, Valoid 50 mg Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the proposed product and the reference product are interchangeable. Clinical experience with cyclizine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the Marketing Authorisation application on 15th July 2011.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 19th July 2011.
3	Following assessment of the application, the MHRA requested further information relating to the dossier on 27th October 2011, 29th May 2012 and 17th August 2012.
4	The applicant responded to the MHRA's requests, providing further information on 2nd January 2012, 16th June 2012 and 29th August 2012.
5	The application was determined on 3rd October 2012.

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS AND PATIENT INFORMATION LEAFLET

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.

LABELLING


Read the package leaflet before use.
Cyclizine Tablets are used to help stop you feeling sick (nausea) or being sick (vomiting).
Dosage
Adults and children over 12 years: Take 1 (one) tablet up to three times daily.
Children from 6 to 12 years: Give half a tablet up to three times a day.
Not recommended for children under 6 years.
Keep out of the reach and sight of children.
Each tablet contains 50mg cyclizine hydrochloride.
Also contains lactose monohydrate.
Keep the blisters in the outer carton in order to protect from light.
Warning: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink.
Varnish free Area for Batch Details EXP. & Lot
MORNINGSIDE HEALTHCARE
MA Holder:Morningside Healthcare Ltd
115 Narbrough Road
Leicester,LE3 0PA, U.K.
PL 20117/0216
100 Tablets
Cyclizine Hydrochloride 50 mg Tablets
Cyclizine Hydrochloride
50mg
MORNINGSIDE HEALTHCARE


Embossing Zone
Cyclizine Hydrochloride 50mg Tablets
Cyclizine Hydrochloride
Morningside Healthcare Ltd
Embossing Zone