Cyclizine Hydrochloride 50mg Tablets
PL 25298/0046

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brown & Burk UK Limited a Marketing Authorisation for the medicinal product Cyclizine Hydrochloride 50mg Tablets (PL 25298/0046) on 11 September 2012. This medicine is a pharmacy (P) medicine, available only from pharmacies under the supervision of a pharmacist and may be used for the following conditions:

- travel and motion sickness
- post-operative nausea and vomiting
- vomiting associated with cancer treatment.

Cyclizine Hydrochloride 50mg Tablets may also be used in the treatment of sickness due to inner ear problems, such as Meniere's disease.

Cyclizine Hydrochloride 50mg Tablets contain the active ingredient cyclizine hydrochloride, which belongs to a group of medicines known as antihistamines. Antihistamines help prevent feelings of sickness (nausea) or being sick (vomiting).

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

Cyclizine Hydrochloride 50mg Tablets
PL 25298/0046

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Brown & Burk UK Limited a Marketing Authorisation for the medicinal product Cyclizine Hydrochloride 50mg Tablets (PL 25298/0046) on 11 September 2012. The product is a pharmacy (P) medicine indicated for:

- 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 Hydrochloride 50mg 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 was submitted under Article 10(1) of Directive 2001/83/EC (as amended), claiming to be a generic medicinal product of Valoid Tablets 50 mg (Amdipharm Plc, UK), which was first authorised in Ireland on 01 April 1979. The corresponding reference product in the UK is Valoid Tablets, which was first authorised in the UK on 29 August 1984.

The active ingredient, cyclizine hydrochloride, is a piperazine derivative, which belongs to the anti-histamine group of drugs. It acts both on the emetic trigger zones and by damping the labyrinthine sensitivity. Pharmacologically, cyclizine hydrochloride has anti-histaminic, antiserotonic, local anaesthetic, and vagolytic actions. Therapeutically, it is an anti-emetic agent.

No new non-clinical data have been submitted, 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.

A single-dose, bioequivalence study was submitted to support this application, comparing the applicant’s test product Cyclizine Hydrochloride Tablets 50 mg (manufactured by Micro Labs Ltd, India) with the reference product Valoid Tablets 50 mg (Amdipharm Plc, UK) under fasting. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

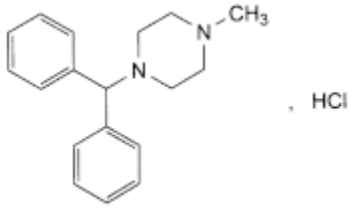
With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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 taking Cyclizine Hydrochloride 50mg Tablets outweigh the risks and a Marketing Authorisation was granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Cyclizine hydrochloride
Chemical Name: 1-(Diphenylmethyl)-4-methylpiperazine hydrochloride
Molecular Formula: $C_{18}H_{22}N_2HCl$
Structure



Molecular weight: 302.8
Appearance: A white or almost white, crystalline powder.
Solubility Slightly soluble in water and in ethanol (96 per cent).

Cyclizine hydrochloride is 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 analysis data are provided and 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.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients maize starch, lactose monohydrate, povidone (PVP K-30), pregelatinised maize starch (Starch 1500) and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate uncoated tablets containing 50 mg cyclizine hydrochloride that could be considered a generic medicinal product of the reference product Valoid Tablets 50 mg (Amdipharm Plc, UK, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the 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. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future production-scale batches.

Control of Finished Product
The finished product specification is satisfactory. 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 tablets are packaged in either:

1. polyvinylchloride/polyvinylidene chloride-aluminium (PVC/PVdC-Aluminium) blisters strips in pack sizes of 1,10, 30, 40, 50, 100 and 500 tablets.
2. polypropylene containers with polypropylene caps containing 100 tablets.

Not all pack sizes may be marketed.

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.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years. This medicinal product does not require any special temperature storage precautions.

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

Bioequivalence
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council 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 the patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

As the pharmacodynamic, pharmacokinetic and toxicological properties of cyclizine hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)

The applicant's 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.

CONCLUSION

The grant of a Marketing Authorisation is recommended.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of cyclizine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

A randomised, open label, single-dose, two-treatment, two-sequence, two-period, crossover study to compare the pharmacokinetics of the test product Cyclizine Hydrochloride Tablets 50 mg (Micro Labs Ltd, India) versus the reference product Valoid Tablets 50 mg (Amdipharm Plc, UK) in healthy adult subjects under fasting conditions.

The subjects were administered a single dose of either the test or the reference product with 240 mL of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results for cyclizine hydrochloride and its demethylated metabolite, norcyclizine, are presented below:

Ln-transformed pharmacokinetic parameters (means, ratios and confidence intervals [CI]) of cyclizine hydrochloride

	Means		Test/Ref Ratio (%)	90% CI
	Cyclizine HCl 50 mg (Test)	Valoid Tabs 50 mg (Reference)		
C_{max} (ng/mL)	23.56	23.19	101.59	94.46-109.26
AUC_{0-72} (ngX hr/mL)	473.95	470.62	100.71	96.97-104.59
AUC_{0-inf} (ngX hr/mL)	550.56	542.56	101.47	97.43-105.68

C_{max} maximum plasma concentration
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity

Ln-transformed pharmacokinetic parameters (means, ratios and confidence intervals [CI]) of Norcyclizine

	Means		Test/Ref Ratio (%)	90% CI
	Cyclizine HCl 50 mg (Test)	Valoid Tabs 50 mg (Reference)		
C_{max} (ng/mL)	13.90	14.16	98.21	92.32-104.48
AUC_{0-72} (ngX hr/mL)	197.45	200.25	98.60	93.69-103.77
AUC_{0-inf} (ngX hr/mL)	251.18	252.58	99.44	94.92-104.18

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to 72 hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity

The *Note for Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. The 90 % confidence intervals of the test/reference ratios for $AUC_{0-72,}$ AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the applicant's test product Cyclizine Hydrochloride Tablets 50mg (Micro Labs Ltd, India) is bioequivalent to the reference product Valoid Tablets 50 mg (Amdipharm Plc, UK) under fasting conditions.

EFFICACY

The efficacy of cyclizine hydrochloride is well-known. No new efficacy data have been submitted and none are required for this type of application.

SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

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.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION

The grant of a Marketing Authorisation is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Cyclizine Hydrochloride 50mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of cyclizine hydrochloride are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant's 50 mg tablet (Micro Labs Ltd, India) and the reference product Valoid Tablets 50 mg (Amdipharm Plc, UK).

SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of cyclizine hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

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 cyclizine hydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.

Cyclizine Hydrochloride 50mg Tablets
PL 25298/0046

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 01 June 2011.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 15 June 2011.

3 Following assessment of the application the MHRA requested further information relating to the dossier on 22 September 2011, 17 February 2012 and 05 May 2012.

4 The applicant responded to the MHRA's requests, providing further information on the dossier on 19 December 2011, 05 March 2012, 01 May 2012, 26 June 2012, 13 July 2012 and 01 August 2012.

5 The application was granted on 11 September 2012.

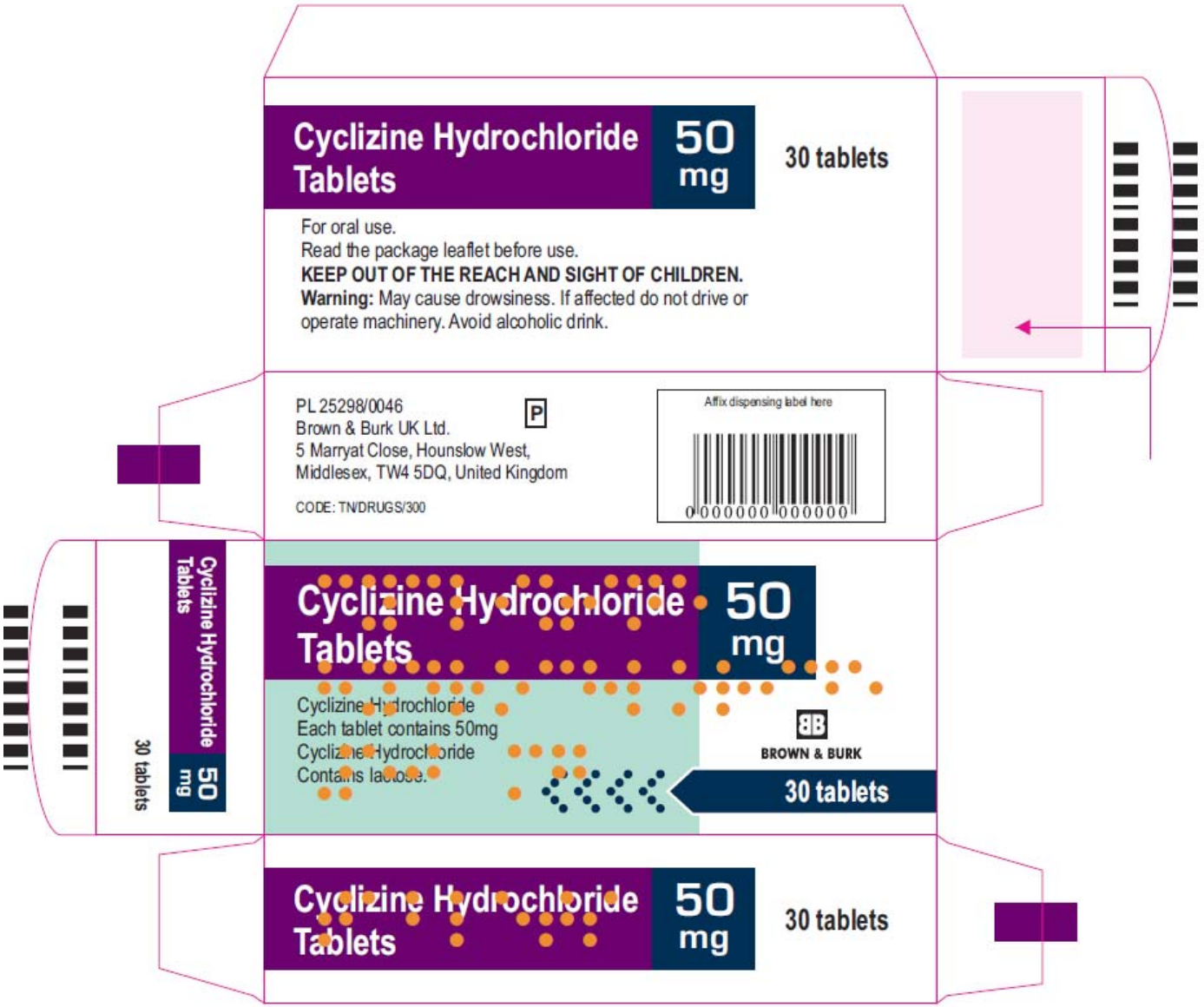
SUMMARY OF PRODUCT CHARACTERISTICS

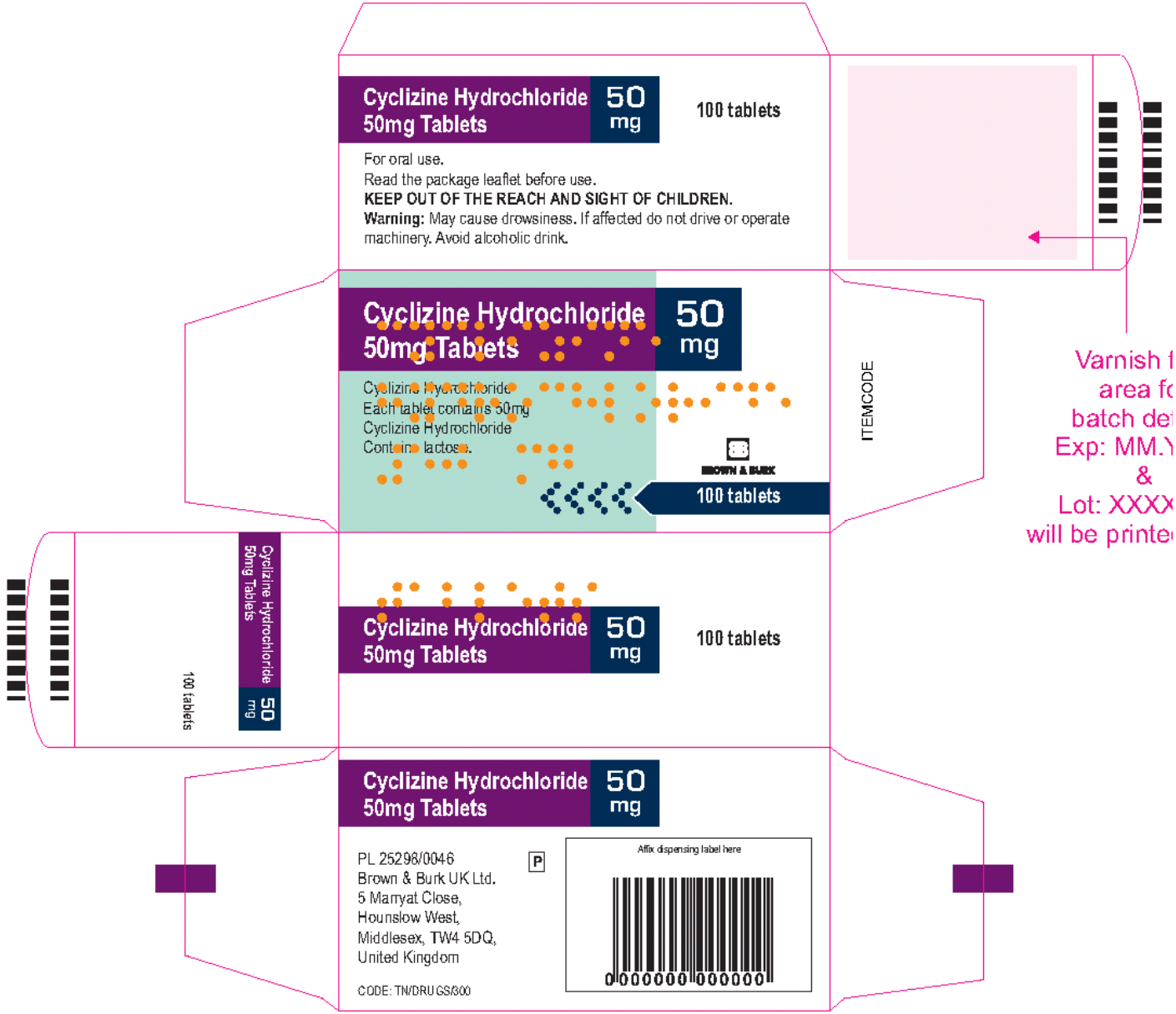
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING


Cyclizine Hydrochloride Tablets
50 mg
30 tablets
For oral use.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Warning: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink.
PL 25298/0046
Brown & Burk UK Ltd.
5 Marryat Close, Hounslow West,
Middlesex, TW4 5DQ, United Kingdom
CODE: TN/DRUGS/300
P
Affix dispensing label here
0 000000 000000
Cyclizine Hydrochloride Tablets
50 mg
30 tablets
Cyclizine Hydrochloride
Each tablet contains 50mg
Cyclizine Hydrochloride
Contains lactose.
BROWN & BURK
30 tablets
Cyclizine Hydrochloride Tablets
50 mg
30 tablets


Cyclizine Hydrochloride 50mg Tablets
50 mg
100 tablets
For oral use.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Warning: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink.
Cyclizine Hydrochloride 50mg Tablets
50 mg
Each tablet contains 50mg Cyclizine Hydrochloride
Contains lactose.
BROWN & BURK
100 tablets
ITEMCODE
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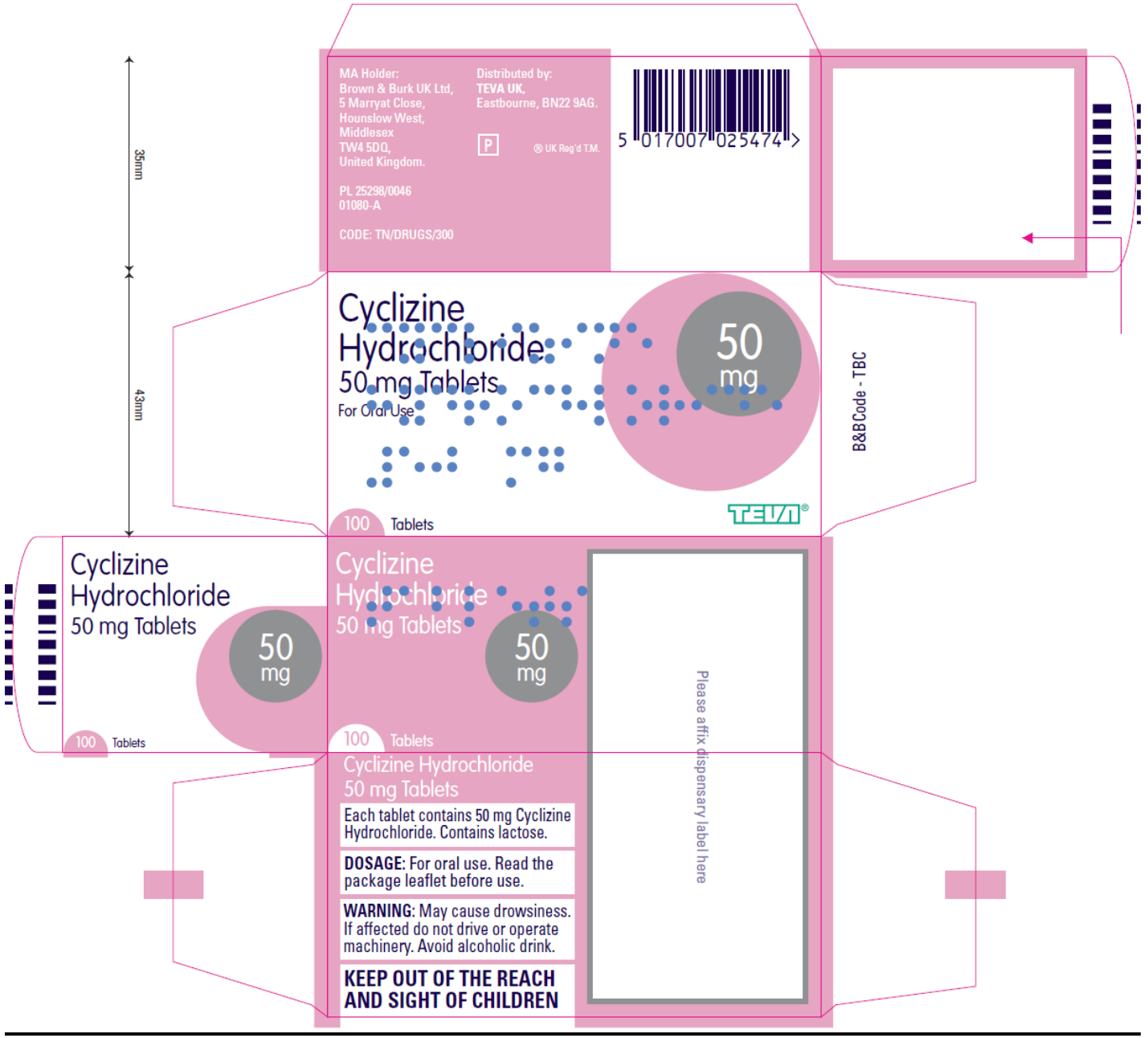
Cyclizine Hydrochloride 50mg Tablets
50 mg
100 tablets
Cyclizine Hydrochloride 50mg Tablets
50 mg
100 tablets
Cyclizine Hydrochloride 50mg Tablets
50 mg
PL 25298/0046
Brown & Burk UK Ltd.
5 Marryat Close,
Hounslow West,
Middlesex, TW4 5DQ,
United Kingdom
CODE: TN/DRUGS/300
P
Affix dispensing label here
0000000 000000


35mm
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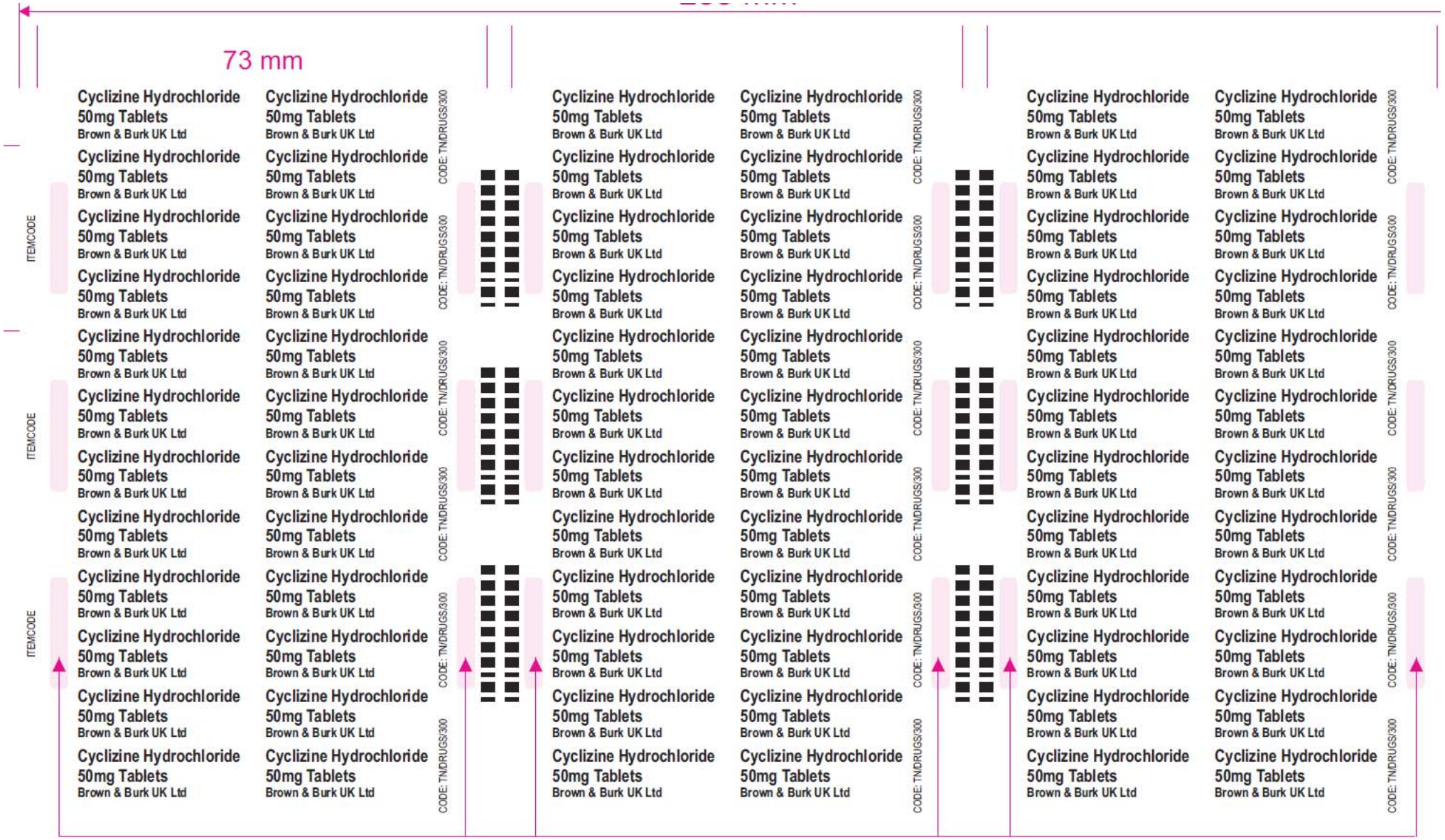
MA Holder:
Brown & Burk UK Ltd,
5 Marryat Close,
Hounslow West,
Middlesex
TW4 5DQ,
United Kingdom.
Distributed by:
TEVA UK,
Eastbourne, BN22 9AG.
® UK Reg'd T.M.
5 017007 025474
PL 25298/0046
01080-A
CODE: TN/DRUGS/300
Cyclizine Hydrochloride
50 mg Tablets
For Oral Use
50 mg
100 Tablets
B&BCode - TBC
Cyclizine Hydrochloride
50 mg Tablets
50 mg
100 Tablets
Please affix dispensary label here
Each tablet contains 50 mg Cyclizine Hydrochloride. Contains lactose.
DOSAGE: For oral use. Read the package leaflet before use.
WARNING: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN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Brown & Burk UK Ltd
ITEMCODE
CODE: TN/DRUGS/300
CODE: TN/DRUGS/600