Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Dicycloverine Hydrochloride 10 mg tablets
Dicycloverine Hydrochloride 20 mg tablets

(dicycloverine hydrochloride)

Procedure No: UK/H/6655/001-002/DC

UK Licence Number: PL 00289/2162-2163

TEVA UK Limited

Lay Summary
Dicycloverine Hydrochloride 10 and 20 mg tablets
(dicycloverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Dicycloverine Hydrochloride 10 and 20 mg tablets (UK/H/6655/001-002/DC; PL 00289/2162-2163). These medicinal products will be collectively referred to as Dicycloverine Hydrochloride Tablets throughout the remainder of the lay summary, for ease of reading.

This summary explains how Dicycloverine Hydrochloride Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products. For practical information about using Dicycloverine Hydrochloride Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Dicycloverine Hydrochloride Tablets and what are they used for?
Dicycloverine Hydrochloride Tablets are 'generic medicines'. This means that Dicycloverine Hydrochloride Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Dicycloverine Hydrochloride 10 and 20 mg Tablets authorised to Winthrop Pharmaceuticals UK Limited (PL 17780/0565-0566).

Dicycloverine Hydrochloride Tablets are used to treat:
- Cramps.
- Pain in the stomach or intestine (gut).
- Stomach or intestine (gut) problems - such as irritable bowel**.**

How do Dicycloverine Hydrochloride Tablets work?
Dicycloverine Hydrochloride Tablets contain an active substance called dicycloverine hydrochloride. This belongs to a group of medicines called antispasmodics.

Dicycloverine hydrochloride works by relaxing the muscles in the stomach and gut (intestine). It stops sudden muscle contractions (spasms). In doing this, it relieves cramps, pain, bloating, wind and discomfort.

How are Dicycloverine Hydrochloride Tablets used?
The pharmaceutical form of this medicine is a tablet, and the route of administration is oral (taken by mouth). The tablets should be swallowed with a glass of water, taken before or after meals.

The patient must always take Dicycloverine Hydrochloride Tablets exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure. The patient's doctor will determine the appropriate doses.

Usual doses:
Dicycloverine Hydrochloride 10 mg Tablets:
Adults and children 12 years of age or older one or two 10 mg tablets 3 times each day.

Children 2 to 11 years of age one 10 mg tablet 3 times each day.

Dicycloverine Hydrochloride 20 mg Tablets:
Adults and children 12 years of age or older one 20 mg tablet 3 times each day.

Children 2 to 11 years of age

Dicycloverine Hydrochloride 20 mg Tablets should not be used in this age group. For administration in this age group, other pharmaceutical strengths/forms may be available.

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

This medicine can only be obtained with a prescription from a doctor.

For further information on how Dicycloverine Hydrochloride Tablets are used, please see the Summaries of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Dicycloverine Hydrochloride Tablets have been shown in studies?
Because Dicycloverine Hydrochloride Tablets are generic medicines, studies have been limited to tests to determine that they are bioequivalent to the reference medicines Dicycloverine Hydrochloride 10 and 20 mg Tablets (Winthrop Pharmaceuticals UK Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Dicycloverine Hydrochloride Tablets?
Because Dicycloverine Hydrochloride Tablets are generic medicines and are bioequivalent to the reference medicines Dicycloverine Hydrochloride 10 and 20 mg Tablets, their benefits and possible side effects are taken as being the same as the reference medicines.

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

Why were Dicycloverine Hydrochloride Tablets approved?
It was concluded that, in accordance with EU requirements, Dicycloverine Hydrochloride Tablets have been shown to have comparable quality and to be bioequivalent to Dicycloverine Hydrochloride 10 and 20 mg Tablets (Winthrop Pharmaceuticals UK Limited). Therefore, the MHRA decided that, as for reference medicines; Dicycloverine Hydrochloride 10 and 20 mg Tablets (Winthrop Pharmaceuticals UK Limited), the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Dicycloverine Hydrochloride Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Dicycloverine Hydrochloride Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Dicycloverine Hydrochloride Tablets, 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 Dicycloverine Hydrochloride Tablets
The UK agreed to grant Marketing Authorisations for Dicycloverine Hydrochloride Tablets on 06 July 2018. No other Member States completed the procedure.

Following a national phase in the UK, Marketing Authorisations were granted to Teva UK Limited on 01 August 2018.

For more information about taking Dicycloverine Hydrochloride Tablets, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Dicycloverine Hydrochloride Tablets follows this summary.

This summary was last updated in September 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Teva UK Limited, Marketing Authorisations for the medicinal products Dicycloverine Hydrochloride 10 and 20 mg tablets (UK/H/6655/001-002/DC; PL 00289/2162-2163) on 1 August 2018. These products are prescription only medicines (POM) indicated for the treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Luxembourg as Concerned Member State (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference products for these applications are Dicycloverine Hydrochloride 10 and 20 mg Tablets first authorised via the national procedure to the marketing authorisation holder (MAH) Aventis Pharma Limited (PL 04425/0035-0081 on 27 September and 13 February 1986, respectively and which subsequently underwent changes of ownership procedures to the current MAH, Zentiva Pharma UK Limited (PL 17780/0565-0566) on 19 April 2011.

These products contain the active substance dicycloverine hydrochloride. Dicycloverine hydrochloride relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via a dual mechanism; a specific anticholinergic effect (antimuscarinic at the ACh-receptor sites), and through a direct effect upon smooth muscle (musculotropic).

With the exception of the bioequivalence study no new non-clinical or clinical studies were submitted, which is acceptable given that these applications were based on being generic medicinal products of reference products that have been in clinical use for over 10 years.

To support these applications a bioequivalence study in healthy volunteers under fasting conditions was submitted. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) 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.

The RMS considered that these applications could be approved at the end of procedure on 06 July 2018. After a subsequent national phase, Marketing Authorisations (PL 00289/2162-2163) were granted in the UK on 01 August 2018.

II QUALITY ASPECTS

II.1 Introduction

The finished products are formulated as tablets. Each tablet contains 10 mg or 20 mg of the active substance dicyloverine hydrochloride. Other ingredients consist of the pharmaceutical excipients: lactose monohydrate, microcrystalline cellulose, pregelatinised (maize) starch and magnesium stearate.

The finished product is available in PVC/Al blisters or PVC/PVdC/Al blisters packaged in cardboard cartons of 100 (10 mg tablets), or 84 (20 mg tablets) tablets.

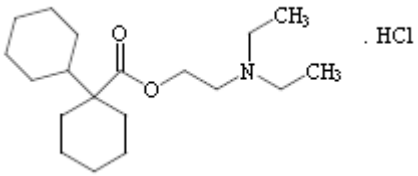
Not all pack sizes may be marketed.

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.

II.2 Drug Substance

INN:	Dicycloverine hydrochloride
Chemical name:	2-(Diethylamino)ethyl[bicyclohexyl]-1-carboxilate Hydrochloride; [Bicyclohexyl]-1-carboxylic acid, 2-(diethlamino)ethyl ester, Hydrochloride.

Structure:



Molecular formula:	$C_{19}H_{35}NO_2$ HCl
Molecular weight:	345.95 g/mol
Appearance:	White or almost white powder
Solubility:	Freely soluble in chloroform, in methyl alcohol, in acetic acid, in 96% alcohol; soluble in water, in acetic anhydride; slightly soluble in ethyl alcohol; practically insoluble in ethyl ether.

Dicycloverine hydrocloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, dicycloverine hydrocloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious tablets containing 10 mg, or 20 mg of the active ingredient dicycloverine hydrochloride per tablet that are generic versions of the reference products Dicycloverine Hydrochloride 10 and 20 mg Tablets (Zentiva Pharma UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with their respective European Pharmacopeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The suppliers of lactose monohydrate have provided a declaration to confirm that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results. A satisfactory commitment that process validation on the maximum commercial batch sizes, for every strength, will also be performed.

Finished Product Specification
The finished product specifications are satisfactory. The test methods have been described and have been adequately validated. Batch data that comply with the release specifications have been provided. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in the packaging proposed for marketing in accordance with current guidelines.

The data from these studies support a shelf life of 18 months for the PVC/Al blisters with the storage condition of 'Do not store above 25◦C', and 2 years for the PVC/PVdC/Al blisters with no special storage conditions. A suitable post approval stability declaration to continue routine stability testing on batches of finished product until the end of shelf life has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of dicycloverine hydrochloride 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.

III.4 Toxicology

The proposed limits are in line with the European Pharmacopoeia monograph for dicycloverine and unknown impurities are below the ICH qualification threshold. Impurities in the drug product are controlled to appropriate limits in ICH Q3B.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Dicycloverine hydrochloride 10 and 20 mg tablets are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical point of view therefore grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of dicycloverine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 dicycloverine hydrochloride.

Based on the data provided, Dicycloverine Hydrochloride Tablets can be considered bioequivalent to the reference products Dicycloverine Hydrochloride 10 and 20 mg Tablets (Zentiva Pharma UK Limited).

IV.2 Pharmacokinetics

In support of these applications, one bioequivalence study was conducted (as detailed below):

STUDY

An open label, randomised, single dose, three-way crossover bioequivalence study of dicycloverine hydrochloride 20mg tablets versus the reference product in healthy human adult subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects received a single dose of Test (T) or Reference (R) product in each period according to a randomisation schedule. Blood samples were collected for plasma levels before dosing and up to and including 24 hours after the drug administration. The washout period between treatment phases was 3 days.

The main pharmacokinetic results are presented below:

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (1)	393.92±169.24	501.96±231.61	98.04±39.33	1.33 (0.67 – 3.00)
Test (2)	392.57±140.99	508.12±196.51	94.12±29.05	1.17 (0.67 – 1.67)
Reference	385.52±141.74	486.28±191.44	88.64±27.60	1.33 (1.00 – 3.00)
***Ratio Test 1 (90% CI)**	99.51 (95.62 – 103.57)	99.89 (94.56 – 105.52)	106.99 (99.70 – 114.82)	
***Ratio Test 2 (90% CI)**	101.51 (97.55 – 105.64)	104.43 (98.87 – 110.31)	106.18 (98.95 – 113.93)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for dicycloverine hydrochloride lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to Dicycloverine Hydrochloride 20 mg Tablets (Winthrop Pharmaceuticals UK Limited (now authorised to Zentiva Pharma Limited).

Biowaiver

As the 10 mg strength test product met the biowaiver criteria specified in the current bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the results and conclusions of the bioequivalence study with the 20 mg strength can be extrapolated to Dicycloverine hydrochloride 10 mg tablets.

IV.4 Clinical efficacy

No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety

Apart from the data from the study stated above, no new clinical safety data are required for these applications and none have been submitted. No new or unexpected safety issues were identified in these clinical studies.

IV.6 Risk Management Plan (RMP)

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC, as amended.

There are no differences from the reference products in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference products, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the national competent authority

- 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.

If the dates for submission of a Periodic Safety Update Report (PSUR) and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

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.

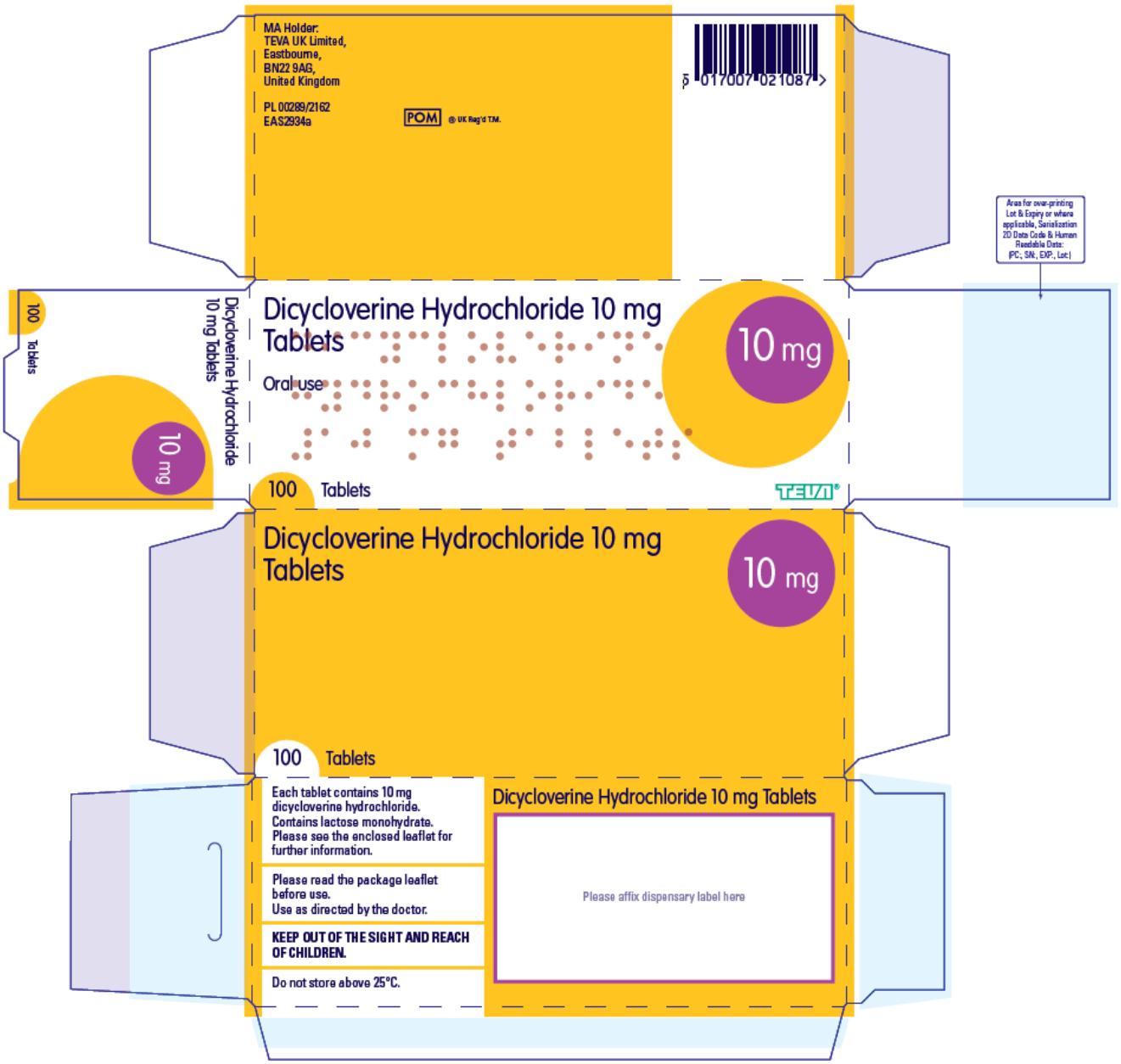
IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

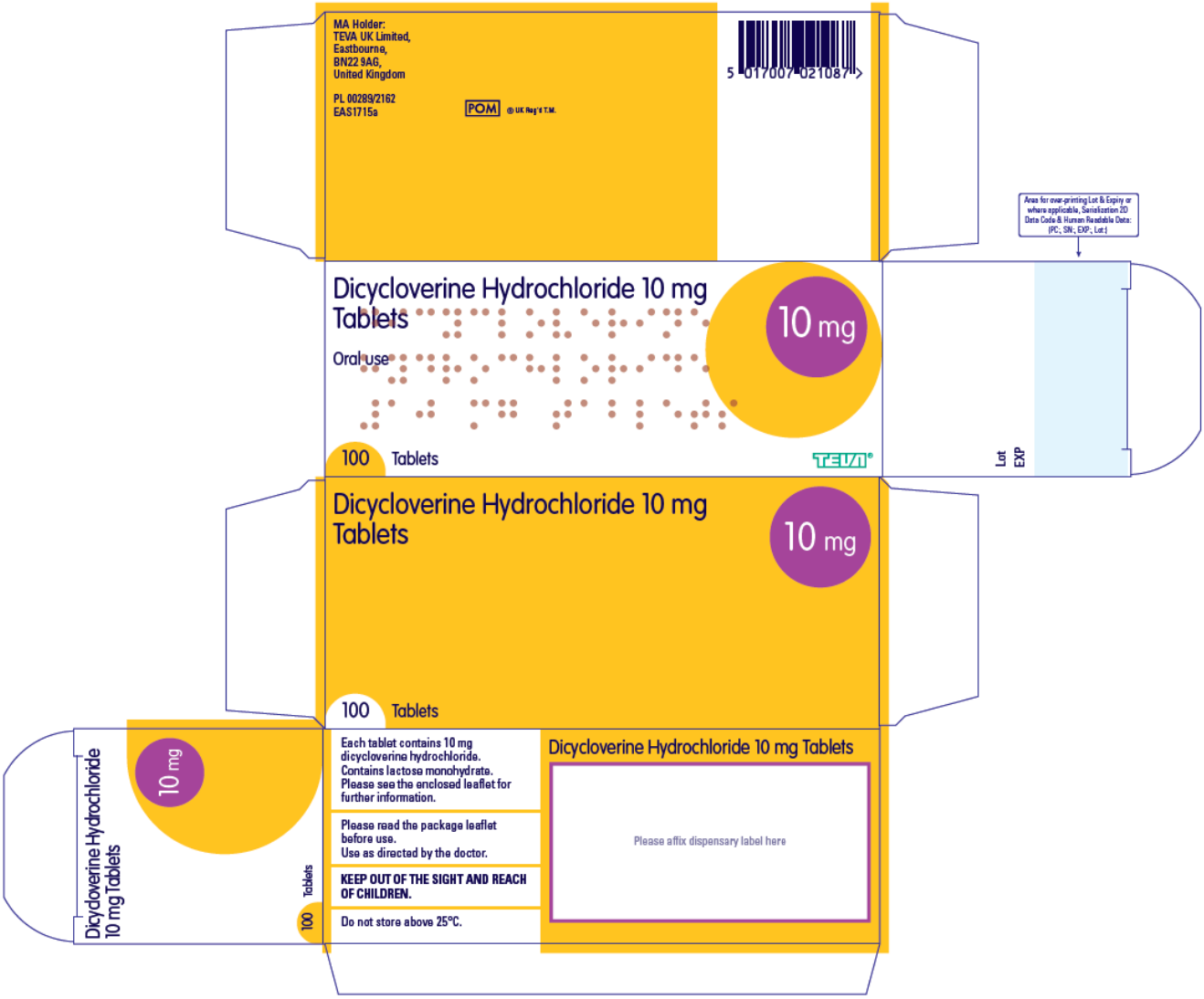
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dicloverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the reference products and its benefit/risk balance is, therefore, considered to be similar and positive.

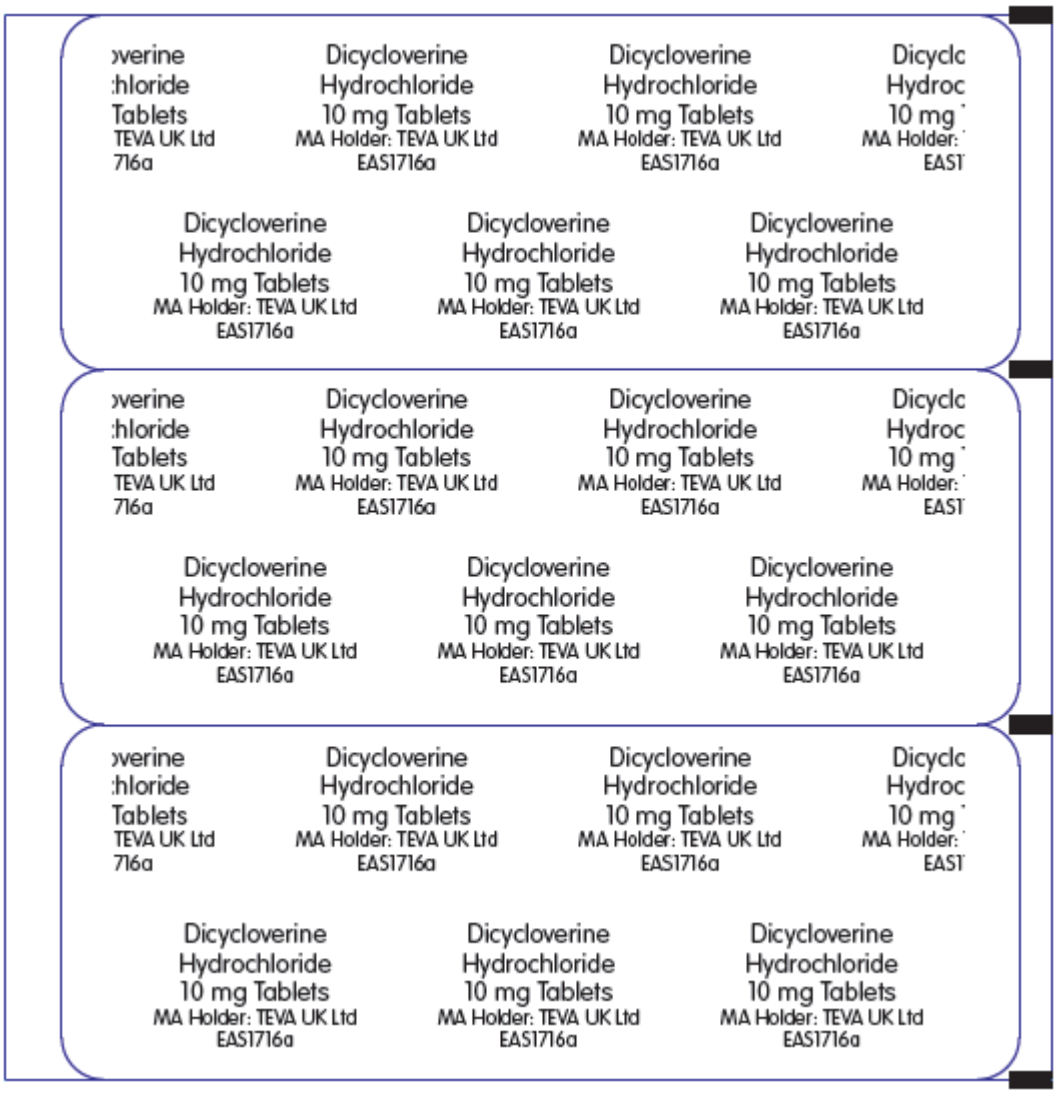
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

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 current approved labelling for these medicines is presented below:




MA Holder:
TEVA UK Limited,
Eastbourne,
BN22 9AG,
United Kingdom
PL 00289/2162
EAS1715a
POM
5 017007 021087
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC; SN; EXP; Lot:)
Dicycloverine Hydrochloride 10 mg Tablets
Oral use
10 mg
100 Tablets
TEVA
Lot
EXP
Dicycloverine Hydrochloride 10 mg Tablets
10 mg
100 Tablets
Each tablet contains 10 mg dicycloverine hydrochloride.
Contains lactose monohydrate.
Please see the enclosed leaflet for further information.
Please read the package leaflet before use.
Use as directed by the doctor.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not store above 25°C.
Dicycloverine Hydrochloride 10 mg Tablets
Please affix dispensary label here
Dicycloverine Hydrochloride 10 mg Tablets
10 mg
100 Tablets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Tablets
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Dicycloverine
Hydrochloride
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MA Holder:
TEVA UK Limited,
Eastbourne,
BN22 9AG,
United Kingdom
PL 00289/2163
EAS2935a
POM
® UK Reg'd T.M.
5 017007 021117
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC:, SN:, EXP:, Lot:)
84 Tablets
Dicycloverine Hydrochloride 20 mg Tablets
20 mg
Dicycloverine Hydrochloride 20 mg Tablets
Oral use
20 mg
84 Tablets
TEVA
Dicycloverine Hydrochloride 20 mg Tablets
20 mg
84 Tablets
Each tablet contains 20 mg dicycloverine hydrochloride.
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Please read the package leaflet before use.
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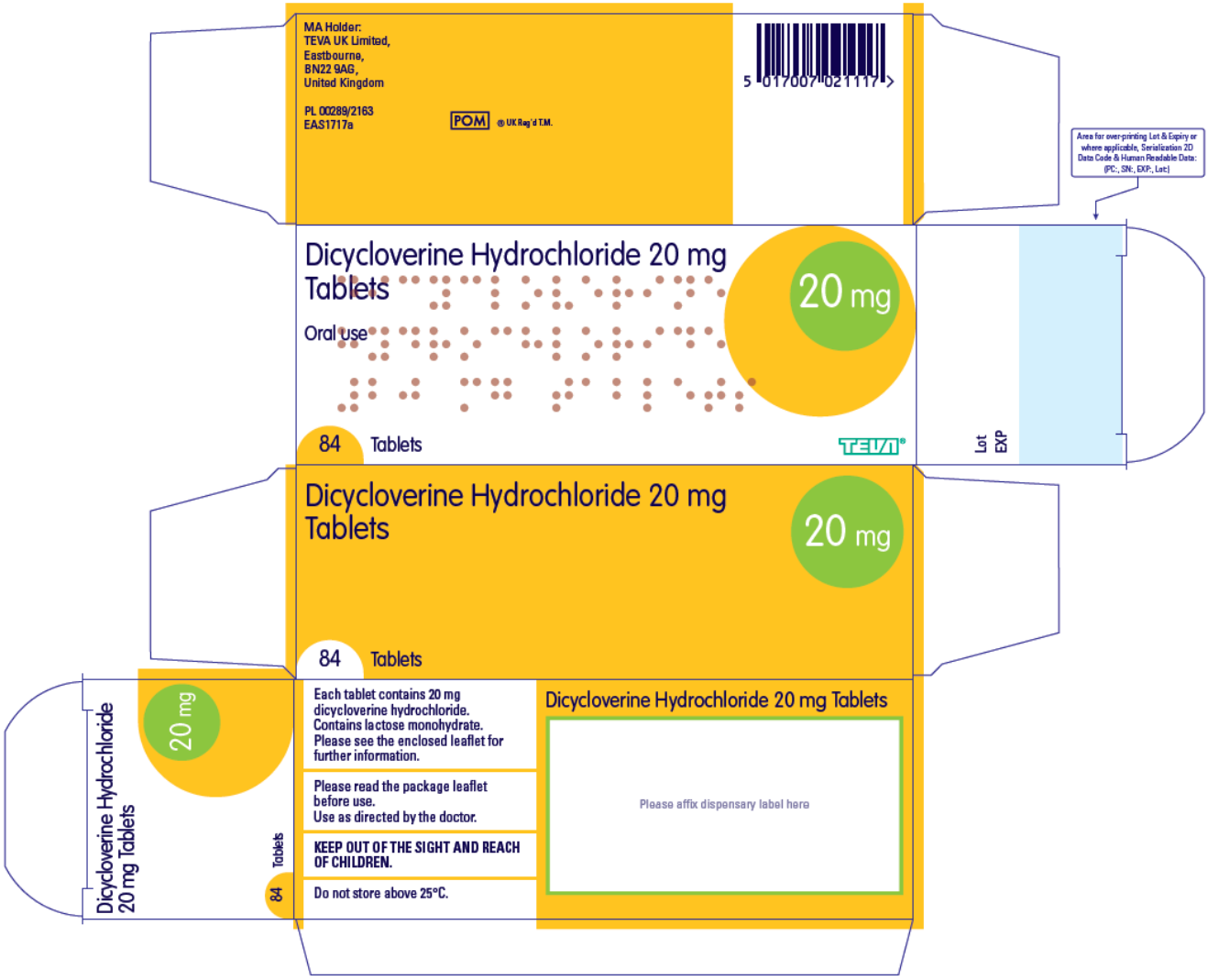
Do not store above 25°C.
Dicycloverine Hydrochloride 20 mg Tablets
Please affix dispensary label here


MA Holder:
TEVA UK Limited,
Eastbourne,
BN22 9AG,
United Kingdom
PL 00289/2163
EAS1717a
POM
® UK Reg'd T.M.
5 017007 021117
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC:, SN:, EXP:, Lot:)
Dicycloverine Hydrochloride 20 mg Tablets
Oral use
20 mg
84 Tablets
TEVA
Lot
EXP
Dicycloverine Hydrochloride 20 mg Tablets
20 mg
84 Tablets
20 mg
Dicycloverine Hydrochloride 20 mg Tablets
84 Tablets
Each tablet contains 20 mg dicycloverine hydrochloride.
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Dicycloverine Hydrochloride 20 mg Tablets
Please affix dispensary label here


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Dicycloverine
Hydrochloride
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MA Holder: TEVA UK Ltd
EAS1718a
Dicycloverine
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MA Holder: TEVA UK Ltd
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EAS1
Dicycloverine
Hydrochloride
20 mg Tablets
MA Holder: TEVA UK Ltd
EAS1718a
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Hydrochloride
20 mg Tablets
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Dicycloverine
Hydrochloride
20 mg Tablets
MA Holder: TEVA UK Ltd
EAS1718a

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)