Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

UKPAR

DICYCLOVERINE HYDROCHLORIDE 10 MG TABLETS
DICYCLOVERINE HYDROCHLORIDE 20 MG TABLETS
(dicycloverine hydrochloride)

UK Licence No: PL 31862/0024-0025

Creo Pharma Limited

LAY SUMMARY

Dicycloverine Hydrochloride 10 mg Tablets
Dicycloverine Hydrochloride 20 mg Tablets
(dicycloverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Dicycloverine Hydrochloride 10 mg Tablets (PL 31862/0024) and Dicycloverine Hydrochloride 20 mg Tablets (PL 31862/0025). It explains how the applications for Dicycloverine Hydrochloride 10 mg and 20 mg 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 Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

For practical information about using Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

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

Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are used to treat cramps, pain in the stomach or intestine (gut), and stomach or intestine (gut) problems such as irritable bowel.

How do Dicycloverine Hydrochloride 10 mg and 20 mg Tablets work?
These medicines contain the active ingredient dicycloverine hydrochloride, which belongs to a group of medicines called antispasmodics. Dicyloverine 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 10 mg and 20 mg Tablets used?
These medicines can only be obtained with a prescription.

Dicycloverine Hydrochloride 10 mg and 20 mg Tablets should be swallowed with a glass of water and can be taken before or after meals.

The usual dose in adults and children 12 years of age or older is one 10 mg tablet or one 20 mg tablet, three times each day. The usual dose in children aged 2 to 11 years of age is one 10 mg tablet three times each day. For children at the younger end of the age range, a tablet is not a suitable dosage form, and Dicycloverine Hydrochloride 10mg/5ml Oral Solution is more appropriate.

What benefits of Dicycloverine Hydrochloride 10 mg and 20 mg Tablets have been shown in studies?
The company provided data from the published literature on the active substance.

Because Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 17780/0565-0566). 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 10 mg and 20 mg Tablets?
Because Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are generic medicines, their possible side effects are taken as being the same as those of the reference medicines, Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 17780/0565-0566).
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For the full list of all side effects reported with Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, see section 4 of the package leaflet.

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

Why were Dicycloverine Hydrochloride 10 mg and 20 mg Tablets approved?
It was concluded that, in accordance with EU requirements, Dicycloverine Hydrochloride 10 mg and 20 mg Tablets have been shown to have comparable quality and to be bioequivalent to Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 17780/0565-0566). Therefore, the MHRA decided that, as for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 17780/0565-0566), the benefits outweigh the identified risks and recommended that Dicycloverine Hydrochloride 10 mg and 20 mg Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Dicycloverine Hydrochloride 10 mg and 20 mg Tablets?
A risk management plan (RMP) has been developed to ensure that Dicycloverine Hydrochloride 10 mg and 20 mg 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 10 mg and 20 mg 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 and reviewed continuously.

Other information about Dicycloverine Hydrochloride 10 mg and 20 mg Tablets
Marketing Authorisations were granted in the UK on 16 October 2018.

The full PAR for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets follows this summary. For more information about treatment with Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, patients should read the package leaflet, or contact their doctor or pharmacist.

This summary was last updated in November 2018.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Creo Pharma Limited Marketing Authorisations for the medicinal products Dicycloverine Hydrochloride 10 mg Tablets (PL 31862/0024) and Dicycloverine Hydrochloride 20 mg Tablets (31862/0025) on 16 October 2018.

These products are prescription only medicines (legal classification POM).

These were applications made under the National Procedure, according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Dicycloverine hydrochloride 10 mg Tablets (PL 17780/0565) and Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566) which were granted Marketing Authorisations to Zentiva Pharma UK Limited on 19 April 2011. This followed changes of ownership from PL 04425/0035 and PL 04425/0081 (also known as Merbentyl 10 and 20 mg Tablets), which were granted Marketing Authorisations to Aventis Pharma Limited on 27 September 1982 and 13 February 1986, respectively.

Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract.

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;
- a direct effect upon smooth muscle (musculotropic).

With the exception of the bioequivalence studies, no new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

A pilot and a pivotal bioequivalence study were performed, which compared the pharmacokinetics of the test product Dicycloverine Hydrochloride 20 mg Tablets to those of the reference product Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566; Zentiva Pharma UK Limited). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

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

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications and these are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

Dicycloverine Hydrochloride 10 mg Tablets are round, biconvex tablets, engraved with “10” on one side and plain on the other. Each tablet contains 10 mg of the active ingredient dicycloverine hydrochloride.

Dicycloverine Hydrochloride 20 mg Tablets are round, biconvex tablets, engraved with “20” on one side and plain on the other. Each tablet contains 20 mg of the active ingredient dicycloverine hydrochloride.

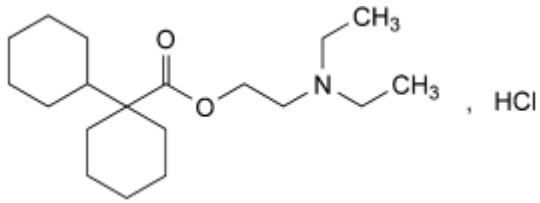
Other ingredients consist of the pharmaceutical excipients, namely povidone K30, maize starch, calcium hydrogen phosphate (anhydrous), lactose monohydrate (140 M) and magnesium stearate.

The finished products are packaged in opaque polyvinyl chloride/polyvinylidene chloride blisters, lidded with aluminium foil. The 10 mg blisters contain 10 tablets and are presented in packs of 100 tablets. The 20 mg blisters contain 14 tablets and are presented in packs of 84 tablets.

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

Ph. Eur.: Dicycloverine hydrochloride
INN: Dicycloverine
Chemical name: 1,1-Bicyclohexyl]-1-carboxylic acid 2-(diethylamino)ethyl esterhydrochloride
2-(Diethylamino)ethyl 1-cyclohexylcyclohexane-1-carboxylatehydrochloride
Structure:



Molecular formula: $C_{19}H_{35}NO_2 \cdot HCl$
Molecular weight: 346
Appearance: White or almost white crystalline powder.
Solubility: Soluble in water, freely soluble in ethanol (96%) and in methylene chloride

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate stable products that could be considered generic medicinal products of the reference products Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 17780/0565-0566).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the applicant’s products versus the reference product.

All the excipients comply with their respective European Pharmacopoeia monographs. With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. The magnesium stearate is of vegetable origin. This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on two batches of each strength/form of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed for each product is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification for each product. 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 18 months for the 10 mg strength and 2 years for the 20 mg strength, with the special storage conditions of "Store below 25°C".

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of dicycloverine hydrochloride are well known. No new non-clinical data have been submitted for these applications 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 these applications and none have been submitted.

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

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

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to dicycloverine hydrochloride is anticipated. Thus, the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

IV. CLINICAL ASPECTS
IV.1 Introduction
With the exception of the bioequivalence studies detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

Pilot study:
A three-period, three-treatment, three-sequence crossover study comparing the pharmacokinetics of two formulations of the test product, Dicycloverine Hydrochloride 20 mg Tablets to those of the reference product Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566; Zentiva Pharma UK Limited), in healthy, adult, human subjects, under fasting conditions.

One of the test formulations was the proposed formulation (of the same batch as in the pivotal study, described below) while the other formulation was a prototype. Bioequivalence was demonstrated in line with the criteria defined in CPMP/EWP/QWP/1401/98 Rev. 1/Corr**. Although not required, the full report was provided by the applicant.

Pivotal study:
A two-period, two-treatment, two-sequence crossover study comparing the pharmacokinetics of the test product, Dicycloverine Hydrochloride 20 mg Tablets to those of the reference product Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566; Zentiva Pharma UK Limited), in healthy, adult, human subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each treatment was separated by a washout period of 7 days.

A summary of the main pharmacokinetic results is presented in the tables below:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	418.619±150.670	540.847±236.864	71.183±19.091	1.500 (0.750 – 5.000)
Reference	390.028±153.786	498.301±232.895	75.748±22.690	1.250 (0.750 – 3.500)
***Ratio Test (90% CI)**	108.50 (101.89 – 115.53)	110.17 (101.17 – 119.96)	95.39 (87.99 – 103.42)	

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

**ln-transformed values*

Compared with the reference product, the 90 % confidence intervals for dicycloverine for the test product are within 80.00-125.00 % for C_{max} and AUC. Dicycloverine Hydrochloride 20 mg Tablets can therefore be considered bioequivalent to Dicycloverine hydrochloride 20 mg tablets (PL 17780/0566).

As these products meet the bio-waiver criteria specified in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength tablets.

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

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

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.
No new or unexpected safety concerns arose from these applications.

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 an 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 Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity reaction to dicycloverine or any of the excipients	SmPC Section 4.3 indicates that patients with a history of allergic reactions to the medicine should not take it.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Increased intraocular pressure particularly in patients with glaucoma or raised intraocular pressure	SmPC Section 4.4 indicates that this medicine should be taken with caution in patients with this condition.	None
Urinary retention, particularly in patients with prostatic hypertrophy	SmPC Section 4.4 indicates that this medicine should be taken with caution in patients with this condition.	None
Aggravated condition when used in patients with hiatus hernia associated with reflux oesophagitis	SmPC Section 4.4 warns that dicycloverine should be used with care in patients with these conditions as this medicine can aggravate the condition.	None
Use of dicycloverine during pregnancy and breastfeeding	SmPC Section 4.6 states that it is not known whether dicycloverine is secreted in breast milk. Therefore, caution is advised.	None

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

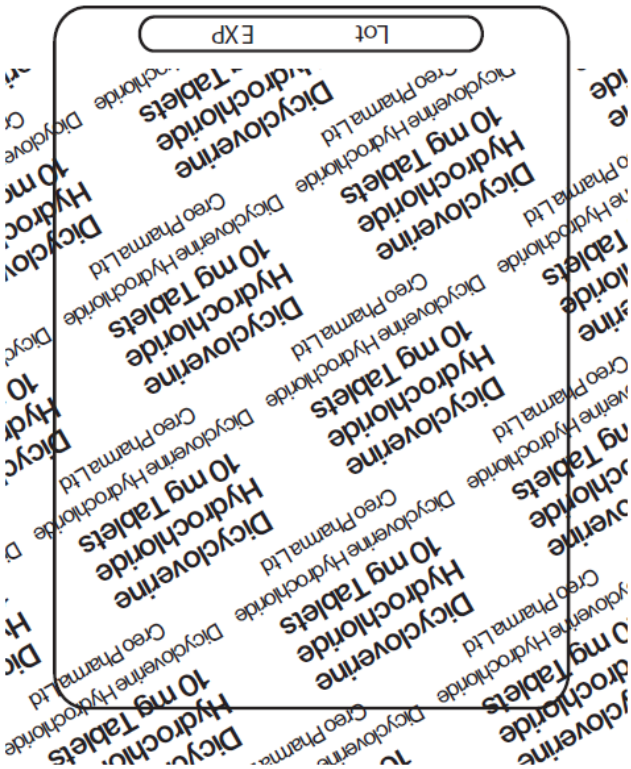
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with dicycloverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

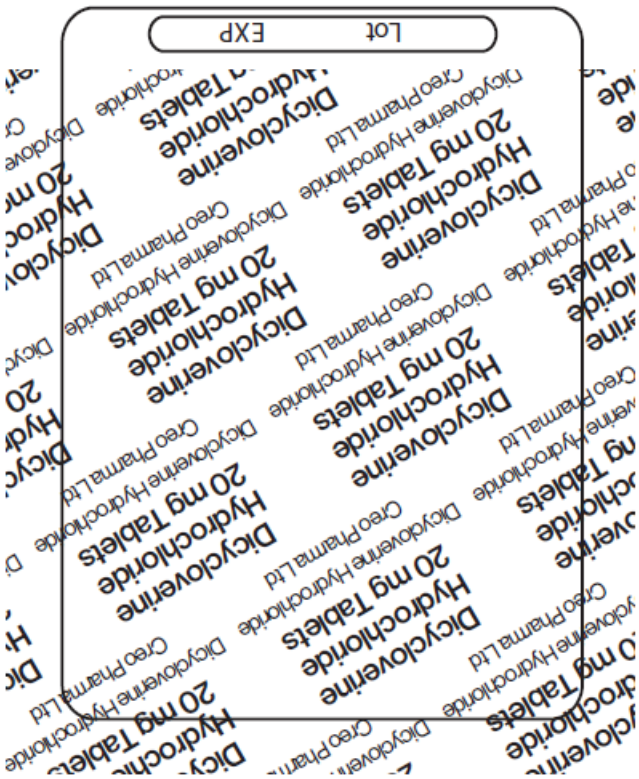
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling is shown below:


Place pharmacy label here
Dicycloverine Hydrochloride
20 mg Tablets
The product also contains lactose.
See the leaflet for further information
For oral use. Use only as directed by a doctor
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Lot:
EXP:
Dicycloverine Hydrochloride
20 mg Tablets
20 mg
ORAL USE
84 tablets
CTE-DCV20-CTN-360
Dicycloverine Hydrochloride
20 mg Tablets
ORAL USE
20 mg
84 tablets
Dicycloverine Hydrochloride
20 mg Tablets
Dicycloverine Hydrochloride
Each tablet contains
20 mg dicycloverine hydrochloride.
20 mg
ORAL USE
84 tablets
Dicycloverine Hydrochloride
20 mg Tablets
MA Holder:
Creo Pharma Ltd
Felsted Business Centre
Felsted, Essex, CM6 3LY, UK
POM
PL 31862/0025
5 060222 601459


Lot
EXP
Dicycloverine Hydrochloride 10 mg Tablets
Creo Pharma Ltd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EXP
Dicycloverine Hydrochloride 20 mg Tablets
Creo Pharma Ltd

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

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)