



Medicines & Healthcare products  
Regulatory Agency

# **Public Assessment Report**

## **National Procedure**

**Dicycloverine Hydrochloride 10 mg Tablets**  
**Dicycloverine Hydrochloride 20 mg Tablets**

**dicycloverine hydrochloride**

**PL 44041/0128-0129**

**Noumed Life Sciences Limited**

## LAY SUMMARY

### Dicycloverine Hydrochloride 10 mg and 20 mg Tablets dicycloverine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets. It explains how these products 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.

These products will be referred to as Dicycloverine hydrochloride tablets in this lay summary for ease of reading.

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?**

These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, a reference medicines already authorised, called Dicycloverine hydrochloride 10mg tablets and 20mg tablets (originally Merbentyl 10 mg and 20mg Tablets).

Dicycloverine hydrochloride tablets are used in the treatment of cramps, pain in the stomach or intestine (gut) and stomach or intestine (gut) problems - such as irritable bowel.

#### **How do Dicycloverine hydrochloride tablets work?**

Dicycloverine hydrochloride tablets contain a medicine called dicycloverine hydrochloride. This belongs to a group of medicines called antispasmodics.

Dicycloverine hydrochloride tablets work by relaxing the muscles in your 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 these medicines is a tablet, and the route of administration is oral (by mouth).

The usual dose is:

##### Adults and children 12 years of age or older

- 10mg: One or two tablets 3 times each day
- 20mg: One tablet 3 times each day

The patient's doctor will tell the patient which dose to use.

##### Children 2 to 11 years of age

- 10mg: One tablet 3 times each day
- Dicycloverine hydrochloride 20mg tablets should not be used in this age group.
- Dicycloverine hydrochloride Syrup is also available for use in this age group

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure

**What benefits of Dicycloverine hydrochloride tablets have been shown in studies?**

Because Dicycloverine hydrochloride tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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?**

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Dicycloverine hydrochloride tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

**Why were Dicycloverine hydrochloride tablets approved?**

It was concluded that, Dicycloverine hydrochloride tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 Dicycloverine hydrochloride tablets?**

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Dicycloverine hydrochloride tablets. The RMP details the important risks of Dicycloverine hydrochloride tablets, how these risks can be minimised, any uncertainties about Dicycloverine hydrochloride tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Dicycloverine hydrochloride tablets:

<b>Summary of safety concerns</b>	
Important identified risks	<ul style="list-style-type: none"> <li>- Eye disorders: blurred vision</li> <li>- Gastrointestinal disorders: dry mouth, constipation, nausea and vomiting</li> <li>- General disorders and administration site conditions: thirst, fatigue</li> <li>- Metabolism and nutrition disorders: anorexia</li> <li>- Nervous system disorders: dizziness, sedation, headache</li> <li>- Renal and urinary disorders: dysuria</li> <li>- Skin and subcutaneous tissue disorders: rash</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>- Hypersensitivity to excipients</li> <li>- Hereditary problems related to excipients</li> </ul>

	<ul style="list-style-type: none"><li>- Caution in patients with hiatus hernia, glaucoma and prostatic hypertrophy</li><li>- Use in Pregnancy</li></ul>
Missing information	<ul style="list-style-type: none"><li>- Use in and Lactation</li></ul>

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Dicycloverine hydrochloride tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

**Other information about Dicycloverine hydrochloride tablets**

Marketing authorisations for Dicycloverine hydrochloride tablets were granted in the United Kingdom (UK) on 03 June 2024.

The full PAR for Dicycloverine hydrochloride tablets follows this summary.

This summary was last updated in June 2024.

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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) considered that the applications for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets (PL 44041/0128-0129) could be approved.

The products are approved for the following indications:

Smooth muscle antispasmodic primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract.

The name of the active substance is dicycloverine hydrochloride, which belongs to the pharmacotherapeutic group of synthetic anticholinergics, esters with tertiary amino groups. Dicycloverine hydrochloride relieves smooth muscle spasms of the gastrointestinal tract.

Animal studies indicate that this action is achieved via a dual mechanism:

- (1) a specific anticholinergic effect (antimuscarinic at the ACh-receptor sites) and
- (2) a direct effect upon smooth muscle (musculotropic).

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of a suitable originator medicinal products, Dicycloverine hydrochloride 10mg tablets and 20mg tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for a generic medicinal products of a suitable reference products.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal product of a suitable reference products. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

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

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

Advice was sought from the Commission of Human Medicines (CHM) on 6 December 2019 following provision of additional data the CHM were reassured on the quality of the product.

Marketing authorisations for Dicycloverine hydrochloride tablets were granted in the United Kingdom (UK) on 03 June 2024.

## II QUALITY ASPECTS

### II.1 Introduction

These products consist of a tablet each table contain 10 mg or 20 mg of dicycloverine hydrochloride. In addition to dicycloverine hydrochloride, these products also contain the excipients lactose monohydrate, calcium hydrogen phosphate anhydrous, maize, starch, sucrose, sodium starch glycolate (Type A), liquid glucose, and magnesium stearate.

The finished products are packaged in blister packs comprised of aluminium foil (20 µm) with PVC white opaque film (250 µm), blisters containing 84 tablets and 100 tablets. Not all pack sizes are marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

### II.2 ACTIVE SUBSTANCE

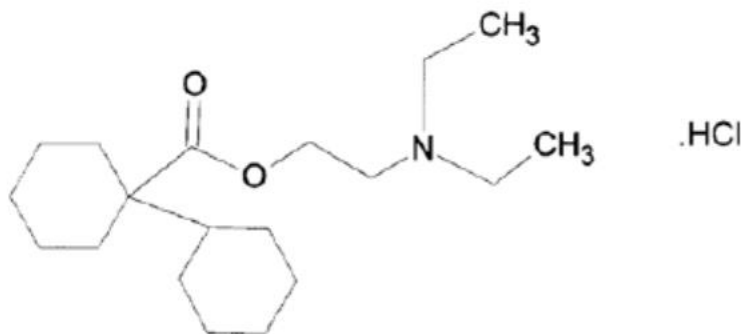
**rINN:** dicycloverine hydrochloride

Chemical Name:

[Bicyclohexyl]-1-carboxylic acid, 2-(diethyl amino) ethyl ester, hydrochloride 2-(Diethylamino)ethyl 1,1'-(bicyclohexane) -1-carboxylate hydrochloride

Molecular Formula:  $C_{19}H_{36}ClNO_2$

Chemical Structure:



Molecular Weight: 346.0

Appearance: White or almost white crystalline powder

Solubility: Soluble in water, freely soluble in ethanol (96 percent) and in methylene chloride

Dicycloverine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

### II.3 DRUG PRODUCTS

#### Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

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

### **Manufacture of the product**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### **Finished Product Specifications**

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

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special precautions for the storage conditions, is acceptable.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

The grant of marketing authorisations was recommended.

## **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.

### **III.2 Pharmacology**

No new pharmacology data were provided, and none were required for these applications.

### **III.3 Pharmacokinetics**

No new pharmacokinetic data were provided, and none were required for these applications.

### **III.4 Toxicology**

No new toxicology data were provided, and none were required for these applications.

### **III.5 Ecotoxicity/Environmental Risk Assessment**

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

### III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction

The clinical pharmacology, efficacy and safety of dicycloverine hydrochloride is well-known. With the exception of data from three bioequivalence studies, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these studies is, thus, satisfactory.

### IV.2 Pharmacokinetics

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

Study BA17629425-01.

This study was an open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral comparing the test product Dicycloverine Hydrochloride 20 mg Tablets versus the reference product Dicycloverine Hydrochloride® 20 mg Tablets in subjects under fasted conditions.

Subjects were administered a single dose of 20 mg dicycloverine tablet with 240 ml of water after an overnight fast of 10 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 10 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

PARAMETER	Test Product: Dicycloverine Hydrochloride 20 mg Tablets		Reference Product: Dicycloverine Hydrochloride® (Dicycloverine Hydrochloride 20 mg Tablets)	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
C <sub>max</sub> (ng/ mL)	23	68.091 ± 23.051 (33.854)	23	70.839 ± 24.799 (35.008)
AUC <sub>t</sub> (ng.hr/ mL)	23	274.199 ± 121.969 (44.482)	23	291.943 ± 117.936 (40.397)
AUC <sub>i</sub> (ng.hr/ mL)	23	319.377 ± 162.416 (50.854)	23	341.095 ± 149.082 (43.707)
AUC <sub>t</sub> /AUC <sub>i</sub>	23	0.879 ± 0.066 (7.545)	23	0.870 ± 0.060 (6.931)
AUC_%Extrap_obs	23	12.036 ± 6.607 (54.896)	23	12.966 ± 6.022 (46.445)
K <sub>el</sub> (1/hr)	23	0.058 ± 0.052 (90.477)	23	0.050 ± 0.060 (120.866)
K <sub>el Lower</sub> (hr)	23	15.228 ± 9.660 (63.433)	23	16.261 ± 8.869 (54.541)
K <sub>el Upper</sub> (hr)	23	39.375 ± 19.728 (50.102)	23	42.303 ± 19.482 (46.053)
NUMPT	23	4.696 ± 3.598 (76.633)	23	4.000 ± 1.595 (39.886)
t <sub>Half</sub> (hr)	23	23.536 ± 19.237 (81.734)	23	26.836 ± 20.988 (78.210)
T <sub>max</sub> (hr)*	23	1.250 (0.750 - 1.750)	23	1.000 (0.750 - 2.000)

The statistical results for primary pharmacokinetic parameters of dicycloverine hydrochloride are summarised below:

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
C <sub>max</sub> (ng/ mL)	23	63.784	23	65.977	96.68
AUC <sub>t</sub> (ng.hr/ mL)	23	250.472	23	268.702	93.22
Pharmacokinetic parameter	90% Confidence Intervals		Acceptance Criteria		Outcome of BE result
C <sub>max</sub> (ng/ mL)	( 89.60%;104.31%)		80.00% - 125.00%		Bioequivalent
AUC <sub>t</sub> (ng.hr/ mL)	( 85.39%;101.76%)		80.00% - 125.00%		

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Study No. BA20629027.

This study was an open label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing the test product Dicycloverine Hydrochloride 10 mg Tablets versus the reference product Dicycloverine Hydrochloride® 10 mg Tablets in healthy adult human subjects under fasted conditions.

Subjects were administered a single dose of 10 mg dicycloverine tablet with 240 ml of water after an overnight fast of 10 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 11 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic data

Pharmacokinetic parameter	Arithmetic Means (±SD) Test product	
	Test Product	Reference product
AUC(0-t)	220.595 (±104.964)	217.931 (±113.311)
AUC (0-∞)	276.122 (±151.806)	276.494 (±178.607)
C <sub>max</sub>	45.988 (±15.911)	46.683 (±17.380)
T <sub>max</sub> <sup>1</sup>	1.385 (0.750 - 2.500)	1.250 (0.750 - 3.000)

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals	CV%
AUC(0-t)	103.17	( 97.25%;109.45%)	12.459
C <sub>max</sub>	99.47	( 93.57%;105.74%)	12.895

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Study No. BA20629028

This study was an open label, randomised, two-period, two-treatment, crossover, single dose oral comparing the test product Dicycloverine Hydrochloride 10 mg Tablets versus the reference product Dicycloverine Hydrochloride® 10 mg Tablets in healthy adult human subjects under fed conditions.

Subjects were administered a single dose of 10 mg dicycloverine tablet with 240 ml of water after an overnight fast of 10 hours, subjects were given a pre-dose standardised high-calories and high-fat breakfast. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 13 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

#### Pharmacokinetic data

Pharmacokinetic parameter	Arithmetic Means ( $\pm$ SD)	
	Test product	Reference Product
AUC(0-t)	303.212 ( $\pm$ 131.206)	307.161 ( $\pm$ 124.937)
AUC(0- $\infty$ )	404.095 ( $\pm$ 224.610)	457.401 ( $\pm$ 384.277)
C <sub>max</sub>	58.312 ( $\pm$ 19.142)	54.353 ( $\pm$ 16.122)
AUC_Extrap_obs	20.752 ( $\pm$ 10.910)	23.576 ( $\pm$ 14.434)
K <sub>el</sub>	0.029 ( $\pm$ 0.035)	0.022 ( $\pm$ 0.015)
T <sub>Half</sub>	44.341 ( $\pm$ 35.743)	56.866 ( $\pm$ 61.966)
T <sub>max1</sub>	2.250 (1.000 - 4.000)	2.250 (1.000 - 5.000)

<sup>1</sup> Median (Min, Max)

#### Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals	CV%
AUC(0-t)	97.32	(89.15%; 106.24%)	18.226
C <sub>max</sub>	105.92	(98.65%; 113.72%)	14.730

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

#### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

#### IV.4 Clinical efficacy

No new efficacy data were submitted with these applications, and none were required.

#### IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

**IV.6 Risk Management Plan (RMP)**

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

**IV.7 Discussion on the clinical aspects**

The grant of marketing authorisations was recommended for these applications.

**V USER CONSULTATION**

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

**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. Extensive clinical experience with dicycloverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

**TABLE OF CONTENT OF THE PAR UPDATE**

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

<b>Application type</b>	<b>Scope</b>	<b>Product information affected</b>	<b>Date of grant</b>	<b>Outcome</b>	<b>Assessment report attached Y/N</b>