IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dicycloverine hydrochloride 10mg/5ml Oral Solution
DICYCLOVERINE HYDROCHLORIDE
PA22697/008/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5520/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 19/11/2018 under procedure number IE/H/0842/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/008/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Dicycloverine (PL 39307/0019; UK/H/5520/001/DC) could be approved. The product is a prescription-only medicine (POM) and is a smooth muscle antispasmodic primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract. The commonest of these are irritable colon (mucous colitis, spastic colon).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Merbentyl Syrup 10mg/5ml /Dicycloverine Hydrochloride 10mg/5ml Syrup, which was originally granted in the UK on 13 July 1983 to Aventis Pharma Limited, UK (PL 04425/0047). The licence subsequently underwent a change of ownership procedure to the current licence holder Winthrop Pharmaceuticals UK Limited, on 19 April 2011 (PL 17780/0564).

Dicycloverine hydrochloride relieves smooth muscle spasm 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).

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous oral solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
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 and CMS considered that the application could be approved at the end of procedure (Day 192) on 15 December 2014. After a subsequent national phase, a licence was granted in the UK on 22 January 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

Each 5ml of solution contains 10mg dicycloverine hydrochloride. Other ingredients consist of the pharmaceutical excipients citric acid monohydrate (E330), sucralose (E955), invert syrup (containing glucose, sucrose and fructose), sodium benzoate (E211), strawberry flavour (containing propylene glycol (E1520) and natural flavouring substances) and purified water. The finished product is packed into amber glass bottles with high-density polyethylene (HDPE), expanded polyethylene (EPE) wadded, tamper evident, child resistant screw on white plastic polypropylene caps and is placed in a cardboard carton together with a double-ended plastic spoon dosing device with 2.5 ml and 5ml measurements at each end. The product is available in pack sizes of 100ml, 120ml and 300ml bottles. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

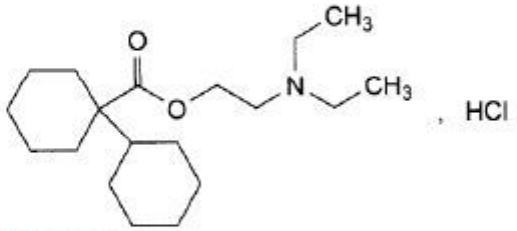
II.2. Drug Substance

INN: Dicycloverine hydrochloride

Chemical name:

2-(diethylamino)ethyl bicyclohexyl-1-carboxylate hydrochloride

Structural formula:



Molecular formula: $C_{19}H_{35}NO_2HCl$.
Molecular mass: 346.0
Appearance: A white or almost white, crystalline powder.
Solubility: Soluble in water, freely soluble in alcohol 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, dicycloverine hydrochloride, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral solution containing 10mg/5ml dicycloverine hydrochloride that was comparable in performance to the originator product Merbentyl Syrup 10mg/5ml /Dicycloverine Hydrochloride 10mg/5ml Syrup (Winthrop

Pharmaceuticals UK Limited, trading as Zentiva, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparable *in-vitro* dissolution profiles have been provided for this product and the reference product.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the strawberry flavour which is controlled to a suitable in-house specification. In addition, confirmation has been provided that the strawberry flavour complies with food regulation EC No.1334/2008. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with no special storage conditions.

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

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

II.5 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.

III. NON-CLINICAL ASPECTS

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

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Dicycloverine is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), "bioequivalence studies are generally not required if the test product is to be administered as an aqueous oral solution containing the same active substance as the currently approved product."

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 can be considered bioequivalent to Merbentyl Syrup 10mg/5ml /Dicycloverine Hydrochloride 10mg/5ml Syrup (Winthrop Pharmaceuticals UK Limited, trading as Zentiva, UK).

IV.2 Pharmacokinetics

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (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 to Dicycloverine.

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

Summary table of safety concerns:

VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	• Known idiosyncratic reactions to dicycloverine hydrochloride • Use in patients with inability to digest certain sugars • Use in patients with hiatus hernia associated with reflux oesophagitis • Use in patients with or suspected of having glaucoma • Use in patients with or suspected of having prostatic hypertrophy • Overdose
Important potential risks	• Use in infants less than 6 months of age
Missing information	• Use in pregnancy and lactation

Summary table of risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Known idiosyncratic reactions to dicycloverine hydrochloride	The risks associated with the use of the drug product in patients with known idiosyncrasy to dicycloverine hydrochloride are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with inability to digest certain sugars	The risks associated with the use of the drug product in patients with inability to digest certain sugars are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	
Use in patients with hiatus hernia associated with reflux oesophagitis	The risks associated with the use of the drug product in hiatus hernia associated with reflux oesophagitis are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with or suspected of having glaucoma	The risks associated with the use of the drug product in patients with or suspected of having glaucoma are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with or suspected of having prostatic hypertrophy	The risks associated with the use of the drug product in patients with or suspected of having prostatic hypertrophy are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Overdose	The risks associated with the overdose of the drug product are described in the SPC, and appropriate advice is provided to the prescriber to minimise these	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	risks.	
Important potential risks		
Use in infants less than 6 months of age	The risks associated with the use of the drug product in infants less than 6 months of age are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Missing information		
Use in pregnancy and lactation	The information in SPC about the drug product use cannot exclude the risk of teratogenicity with absolute certainty, so it should be used during pregnancy only if clearly needed. Also, it is not known whether dicycloverine is secreted in human breast milk, so caution should be exercised when dicycloverine is administered to a nursing mother.	Not applicable

No new risks have been identified for this generic product, which are not recognised for the reference product. Overall, the proposed RMP has adequately captured the important identified and potential risks associated with the drug substance.

IV.7 Discussion on the clinical aspects

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous oral solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application.

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.*

V. OVERALL CONCLUSIONS

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product 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.

VI. REVISION DATE

24/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5520/1/DC to IE/H/0842/1/DC			