IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Nytol One-A-Night 50 mg Tablets
DIPHENHYDRAMINE HYDROCHLORIDE
PA1186/016/001

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/6071/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 14th January 2019 under procedure number IE/H/0899/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/016/001
Marketing Authorisation Holder: Chefaro Ireland DAC

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.

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Diphenhydramine 50mg Tablets (PL 02855/0238; UK/H/6071/001/DC), is approvable. This pharmacy medicine (P) is indicated as a symptomatic aid to the relief of temporary sleep disturbance in adults.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, France, Poland, Portugal, Republic of Ireland and Spain as Concerned Member States (CMS). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Diphenhydramine is an ethanolamine-derivative antihistamine. It has anticholinergic and marked sedative effects. It acts by inhibiting the effects on H1-receptors.

Diphenhydramine is effective in reducing sleep onset (i.e., time to fall asleep) and increasing the depth and quality of sleep.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

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

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type 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 Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 12 January 2017). Following a national phase, the UK granted a Marketing Authorisation (PL 02855/0238) for this product on 07 February 2017.

II. QUALITY ASPECTS

II.1 Introduction

Each tablet contains 50mg diphenhydramine hydrochloride (equivalent to 43.8mg diphenhydramine base). The excipients present in this product are lactose anhydrous, stearic acid, microcrystalline cellulose, colloidal anhydrous silica and maize starch.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is lactose anhydrous. The applicant has provided a declaration that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as for human consumption.

The finished product is packaged into rigid unplasticized polyvinylchloride (UPVC)/polyvinylidenechloride (PVdC) blister packs with a heat sealable aluminium foil containing 4, 8, 10, 16 or 20 tablets. Not all pack sizes may be marketed.

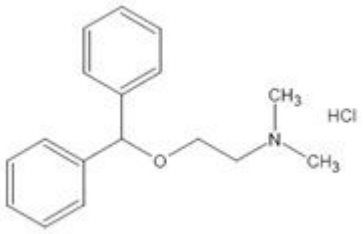
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Diphenhydramine hydrochloride

Chemical name(s): Ethanamine, 2-(diphenylmethoxy)-N-Ndimethyl-Hydrochloride
2-(Diphenylmethoxy)-N,NDimethylethylamine-Hydrochloride

Structure:



Molecular formula: $C_{17}H_{21}NO \cdot HCl$

Molecular weight: 291.82 g/mol

Appearance: White or almost white crystalline powder.

Solubility: Diphenhydramine hydrochloride is very slightly soluble in benzene and diethyl ether, sparingly soluble in acetone, freely soluble in alcohol and chloroform and very soluble in water.

Diphenhydramine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, diphenhydramine hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The aim of the development programme was to formulate safe, efficacious and stable tablets containing 50 mg of diphenhydramine hydrochloride.

Dissolution profiles were provided but since this is an original product itself, there is no comparison with any other 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 and has shown satisfactory results. Process validation data on full scale batches have been provided. The results are satisfactory.

Finished Product Specification

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

Stability of the product

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

Based on the results, a shelf-life of 2 years with storage conditions "Store below 25ºC" and "Store in the original packaging in order to protect from light and moisture" have been set. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacological, pharmacokinetic and toxicological properties of diphenhydramine hydrochloride are well known. As this active substance is well known, no further studies are required and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier. No new non-clinical data have been supplied with this application. This is acceptable.

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)
The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
Diphenhydramine is a widely used and well-known active substance. The details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

IV.2 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

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

IV.4 Clinical efficacy
The efficacy of diphenhydramine hydrochloride is well recognised. No new efficacy data are presented for this application and none are required. However, the applicant has provided a review of study reports published in the literature confirming the efficacy regarding the use of diphenhydramine.

Data within the published medical literature support an acceptable level of safety and efficacy of oral diphenhydramine hydrochloride for the proposed indication. Over 4,800 published references are available on the United States (US) National Library of Medicines (PubMed®) database and from other reputable sources, relating to diphenhydramine and over 360 clinical publications relating to a sedative effect. Literature specific to the sedative effect was first published in the 1950s. Standard medical texts have discussed diphenhydramine's effectiveness in reducing sleep onset (latency, i.e. the time taken to fall asleep) and in increasing the depth and quality of sleep for several years, highlighting its long-standing status as a sleep aid. The review of the literature demonstrates the claim for 'well-established use'.

IV.5 Clinical safety

The clinical overview has provided a satisfactory literature safety review of diphenhydramine. Oral diphenhydramine has been approved and marketed for the relief of temporary sleep disturbances in the UK for more than 20 years.

Nytol periodic safety update report (PSUR) data provides further evidence of the well-established use of oral diphenhydramine in the relief of temporary sleep disturbance.

Worldwide cumulative post-marketing exposure of diphenhydramine is calculated to be approximately 40.4 million individuals during the period from 2002 to 2012.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder has submitted a risk management plan, 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 Diphenhydramine 50mg Tablets.

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

Safety concern (identified)	Routine risk minimisation measures	Additional risk minimisation measures
Drowsiness and sedation - effects on ability to drive and use machines	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.7 Effects on ability to drive and use machines** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.
Use in patients with stenosing peptic ulcer or pyloroduodenal obstruction	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.

Use in patients with myasthenia gravis	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction**	None proposed.
Use in patients with epilepsy or seizure disorders	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.
Use in patients with narrow-angle glaucoma	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.7 Effects on ability to drive and use machines** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.
Use in patients with prostatic hypertrophy or urinary retention	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.
Use in patients with asthma, bronchitis or chronic obstructive pulmonary disease (COPD)	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.

Tolerance	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use**	None proposed.
Potentiation of sedative effects of alcohol	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions of use** **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.7 Effects on ability to drive and use machines** **Section 4.8 Undesirable effects** **Section 4.9 Overdose**	None proposed.
Concomitant use of other antihistamine-containing preparations	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.5 Interaction with other medicinal products and other forms of interaction**	None proposed.
Torsade de pointes/QT prolongation	Safety information in the reference safety information: **Section 4.5 Interaction with other medicinal products and other forms of interaction** **Section 4.9 Overdose**	None proposed.
Use in the elderly	Safety information in the reference safety information: **Section 4.2 Posology** **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects**	None proposed.
Drug abuse and dependence	Safety information in the reference safety information: **Section 4.2 Posology**	None proposed.
	Section 4.4 Special warnings and precautions for use **Section 4.9 Overdose**	
Use during pregnancy and lactation	Safety information in the reference safety information: **Section 4.6 Fertility, pregnancy and lactation**	None proposed.
Effects on fertility	Safety information in the reference safety information: **Section 4.6 Fertility, pregnancy and lactation**	None proposed.
Paediatric use	Safety information in the reference safety information: **Section 4.2 Posology and method of administration**	None proposed.

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V. OVERALL CONCLUSIONS

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 patient information leaflet (PIL) was English.

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*.

OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with diphenhydramine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit risk is, therefore, considered to be positive.

VI. REVISION DATE

September 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6071/001/DC to IE/H/899/001/DC	N/A	N/A	N/A	Approved 14/01/2019