Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Diphenhydramine Hydrochloride 25 and 50 mg Tablets

(diphenhydramine hydrochloride)

Product Licence Numbers: PL 43461/0065-66

Flamingo Pharma UK Ltd

LAY SUMMARY

Diphenhydramine Hydrochloride 25 and 50 mg Tablets

(diphenhydramine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Diphenhydramine Hydrochloride 25 and 50 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 Diphenhydramine Hydrochloride Tablets in this lay summary for ease of reading.

For practical information about using Diphenhydramine Hydrochloride Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Diphenhydramine Hydrochloride Tablets and what are they used for?
These applications are for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Diphenhydramine Hydrochloride Tablets are used to aid relief of temporary sleep disturbance (difficulties sleeping) in adults and children over 16 years of age.

How do Diphenhydramine Hydrochloride Tablets work?
Diphenhydramine Hydrochloride Tablets contains the active ingredient diphenhydramine hydrochloride, which is an antihistamine with sedative properties which induces drowsiness or sedation. It works by reducing the time needed to fall asleep and increases the depth and quality of sleep.

How are Diphenhydramine Hydrochloride Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The tablets should be swallowed whole with water.

The recommended dose is:
Adults and children over 16 years:
25 mg strength tablets: take two tablets 20 minutes before going to bed.
50 mg strength tablets: take one tablet 20 minutes before going to bed.
Patients should not exceed the stated dose. They should not continue to take it for longer than 2 weeks without consulting a doctor.

Use in children:
These products must not be used in children under 16 years of age.

For further information on how Diphenhydramine Hydrochloride Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can be obtained without a prescription.

The patient should always take the 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 Diphenhydramine Hydrochloride Tablets have been shown in studies?
As the active substance diphenhydramine hydrochloride has been in clinical use for over 10 years, data were provided in the form of literature references to show that Diphenhydramine Hydrochloride Tablets are a safe and efficacious treatment for temporary sleep disturbance.

What are the possible side effects of Diphenhydramine Hydrochloride Tablets?
The common side effects with Diphenhydramine Hydrochloride Tablets (may affect up to 1 in 10 people):

- Sedation, drowsiness, dizziness, unsteadiness, disturbance in attention
- Dry mouth
- Fatigue

Other effects:

- Palpitation (feeling the heartbeat)
- Headache, tingling or numbness (pins and needles)
- Depression, sleep disturbances
- Confusion, excitation e.g. increased energy, restlessness, nervousness (the elderly are more likely to experience these effects)
- Difficulty urinating or inability to pass urine
- Thicker bronchial mucus
- Blurred vision
- Feeling or being sick, stomach problems
- Muscle twitching

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Diphenhydramine Hydrochloride Tablets approved?
It was concluded that the data provided from literature references had shown that Diphenhydramine Hydrochloride Tablets are effective in the treatment of temporary sleep disturbance. Furthermore, use of the active substance diphenhydramine hydrochloride in the European Union has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that 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 Diphenhydramine Hydrochloride Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Diphenhydramine Hydrochloride Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 Diphenhydramine Hydrochloride Tablets
Marketing Authorisations for Diphenhydramine Hydrochloride Tablets were granted in the UK on 03 September 2020.

The full PAR for Diphenhydramine Hydrochloride Tablets follows this summary.

This summary was last updated in October 2020.

TABLE OF CONTENTS

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 Diphenhydramine Hydrochloride 25 and 50 mg Tablets (PL 43461/0065-66) could be approved.

The products are approved as an aid to the relief of temporary sleep disturbance.

Diphenhydramine is an ethanolamine-derivative antihistamine. It is an antihistamine with 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.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

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.

National marketing authorisations were granted in the UK on 03 September 2020.

II QUALITY ASPECTS

II.1 Introduction

These products consist of tablets. Each tablet contains 25 or 50 mg of diphenhydramine hydrochloride as active substance.

In addition to diphenhydramine hydrochloride, these products also contain the excipients lactose monohydrate, maize starch and magnesium stearate.

The finished products are packaged in blister packs of aluminium- polyvinylchloride (PVC)/polyvinylidenechloride (PVdC) foil of 12's, 16's and 20's along with a leaflet inside.

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.

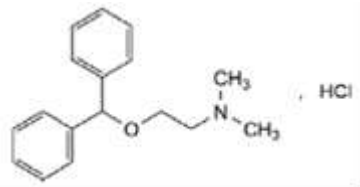
II.2 ACTIVE SUBSTANCE

rINN: Diphenhydramine Hydrochloride

Chemical Name: 2-(Diphenylmethoxy)-N,N-dimethylethanamine hydrochloride

Molecular Formula: $C_{17}H_{21}NO.HCl$

Chemical Structure:



Molecular Weight: 291.8 g/mol

Appearance: White or almost white crystalline powder.

Solubility: Diphenhydramine hydrochloride is very soluble in water and freely soluble in alcohol.

Diphenhydramine 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 has been provided.

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

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

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

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

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

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

Finished Product Specifications
The finished product specifications 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 2 years, with no special storage conditions is approved.

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
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
Slow wave sleep-inducing effects of first generation H1-antagonists were studied in rats. The H1-antagonists used in this study resulted in a decrease in sleep latency and an increase in sleep duration (slow wave sleep). The rate of REM (rapid eye movement) sleep during slow wave sleep was decreased by H1-antagonists and brotizolam. The order of potency of H1-antagonists for the reduction in sleep latency (from greatest to least) was promethazine>chlorpheniramine>diphenhydramine and pyrilamine, and that for the increase in sleep duration was chlorpheniramine>promethazine>diphenhydramine and pyrilamine.

These results clearly showed that H1-antagonists are effective in mild to moderate insomnia as sedative-hypnotic drugs.

III.3 Pharmacokinetics
Studies conducted to characterise the pharmacokinetics of diphenhydramine in non-clinical species. Metabolism has been extensively examined and results indicate extensive metabolite formation. Results showed that diphenhydramine, is transported between blood, brain and

cerebrospinal fluid, in part, by saturable, carrier-mediated transport processes at both the blood-brain and blood cerebrospinal fluid barriers.

III.4 Toxicology

The general toxicity, mutagenicity, carcinogenicity and reproductive potential of diphenhydramine has been adequately described from the available literature.

There is a discussion in the non-clinical overview of the safety of excipients and impurities in the drug products and drug substance which was adequate.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for products containing an active substance of well-established use that will be used in place of existing 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

Pharmacodynamic, pharmacokinetic and toxicological properties of diphenhydramine hydrochloride are well known. As this is a well-known active substance, the applicant has not provided additional studies and further studies are not required. The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.
However, the applicant has provided data that bridges the proposed products with the literature provided to support the efficacy and safety.

IV. 2 Pharmacokinetics

The pharmacokinetics of diphenhydramine has been adequately described in the literature and current reference texts. Special populations (elderly and children) and drug interactions have also been discussed.

IV.3 Pharmacodynamics

The pharmacodynamics of diphenhydramine hydrochloride have been adequately described in the literature and current reference texts.

IV.4 Clinical efficacy

The literature provided d the efficacy of diphenhydramine hydrochloride in the proposed indication and at the proposed posology in adults (including the elderly) and children.

IV.5 Clinical safety

The safety of diphenhydramine hydrochloride has been adequately discussed in the clinical overview. The applicant has also provided bibliographic evidence on general safety of the products.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, 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 Applicant has provided an updated overview which contains a discussion on how the proposed products intended for marketing (Diphenhydramine 25 mg and 50 mg Tablets) and a marketed product (Diphenhydramine 25 mg and 50 mg Tablets) used to demonstrate the pharmaceutical equivalence has the same active substance (diphenhydramine hydrochloride), with the same salt form (hydrochloride), same dosage form (tablet) and same strengths (25 mg and 50 mg), as those of the products cited in the scientific literatures submitted.
No specific brand is quoted in the literature to which specific reference can be made. However, since proposed formulations do not contain any excipients that may affect gastro intestinal (GI) motility or transport proteins and the drug substance, diphenhydramine hydrochloride, is classified as a BCS Class I drug, (high solubility and high permeability), it can be assumed that the proposed products should not behave differently from the products in the literature.

Furthermore, the dissolution profiles and qualitative formulations of the proposed products are similar to the dissolution profiles and qualitative formulations of other currently authorised products.

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL)has been performed on the basis of a bridging report making reference to Diphenhydramine hydrochloride 25 and 50 mg tablets (PL 20416/0067-8; Crescent Pharma Limited) and for the purpose of bridging the layout, Diphenhydramine 50 mg tablets (PL 02855/0238; Omega Pharma Limited). The bridging report submitted by the applicant is acceptable.

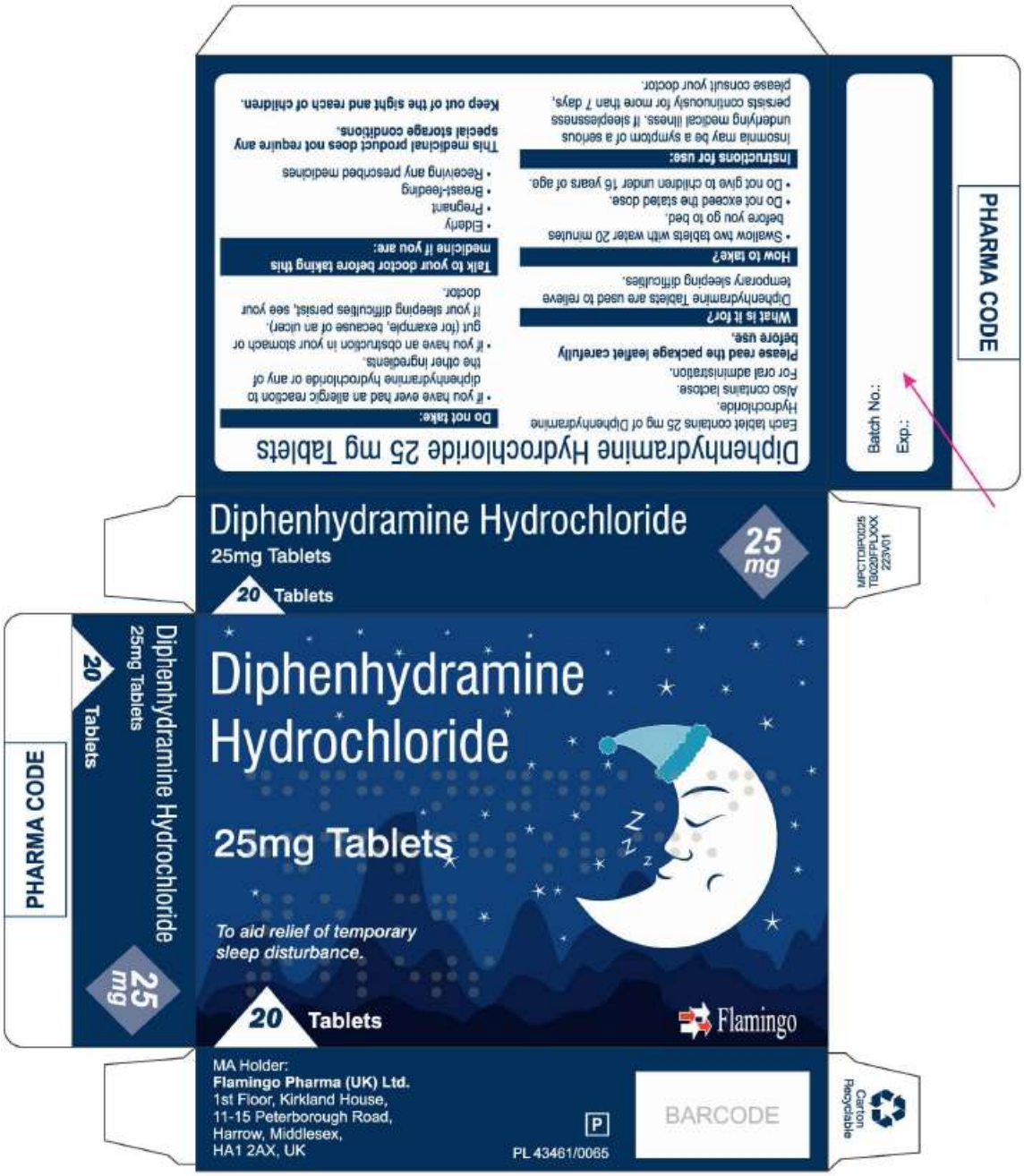
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

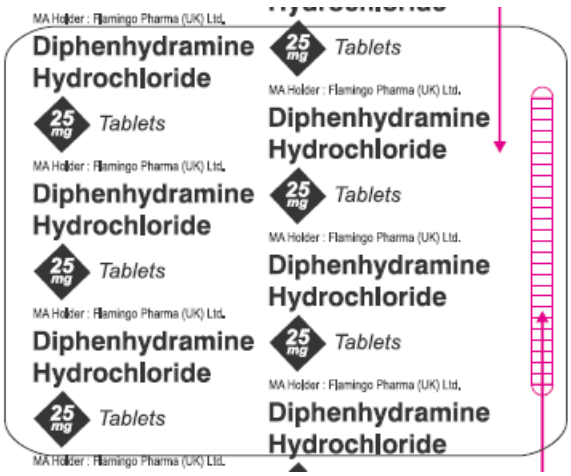
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with diphenhydramine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


Diphenhydramine Hydrochloride 25 mg Tablets
Each tablet contains 25 mg of Diphenhydramine Hydrochloride.
Also contains lactose.
For oral administration.
Please read the package leaflet carefully before use.
What is it for?
Diphenhydramine Tablets are used to relieve temporary sleeping difficulties.
How to take?
• Swallow two tablets with water 20 minutes before you go to bed.
• Do not exceed the stated dose.
• Do not give to children under 16 years of age.
Instructions for use:
Insomnia may be a symptom of a serious underlying medical illness. If sleeplessness persists continuously for more than 7 days, please consult your doctor.
Do not take:
• If you have ever had an allergic reaction to diphenhydramine hydrochloride or any of the other ingredients.
• If you have an obstruction in your stomach or gut (for example, because of an ulcer).
If your sleeping difficulties persist, see your doctor.
Talk to your doctor before taking this medicine if you are:
• Elderly
• Pregnant
• Breast-feeding
• Receiving any prescribed medicines
This medicinal product does not require any special storage conditions.
Keep out of the sight and reach of children.
Batch No.:
Exp.:
PHARMA CODE
MPCTDIP0025 T0023FPLXXX 223V01
Diphenhydramine Hydrochloride
25mg Tablets
20 Tablets
25 mg
Flamingo
MA Holder:
Flamingo Pharma (UK) Ltd.
1st Floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA1 2AX, UK
PL 43461/0065
BARCODE
Carton Recyclable


MA Holder : Flamingo Pharma (UK) Ltd.
Diphenhydramine Hydrochloride
25 mg Tablets


Diphenhydramine Hydrochloride
50mg Tablets
20 Tablets
50 mg
Diphenhydramine Hydrochloride
50mg Tablets
To aid relief of temporary sleep disturbance.
20 Tablets
Flamingo
PHARMA CODE
Batch No.:
Exp.:
Diphenhydramine Hydrochloride 50 mg Tablets
Each tablet contains 50 mg of Diphenhydramine Hydrochloride.
Also contains lactose.
For oral administration.
Please read the package leaflet carefully before use.
What is it for?
Diphenhydramine Tablets are used to relieve temporary sleeping difficulties.
How to take?
• Swallow one tablet with water 20 minutes before you go to bed.
• Do not exceed the stated dose.
• Do not give to children under 16 years of age.
Instructions for use:
Insomnia may be a symptom of a serious underlying medical illness. If sleeplessness persists continuously for more than 7 days, please consult your doctor.
Do not take:
• If you have ever had an allergic reaction to diphenhydramine hydrochloride or any of the other ingredients.
• If you have an obstruction in your stomach or gut (for example, because of an ulcer).
If your sleeping difficulties persist, see your doctor.
Talk to your doctor before taking this medicine if you are:
• Elderly
• Pregnant
• Breast-feeding
• Receiving any prescribed medicines
This medicinal product does not require any special storage conditions.
Keep out of the sight and reach of children.
MA Holder:
Flamingo Pharma (UK) Ltd.
1st Floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA1 2AX, UK
PL 43461/0066
BARCODE
Carton Recyclable

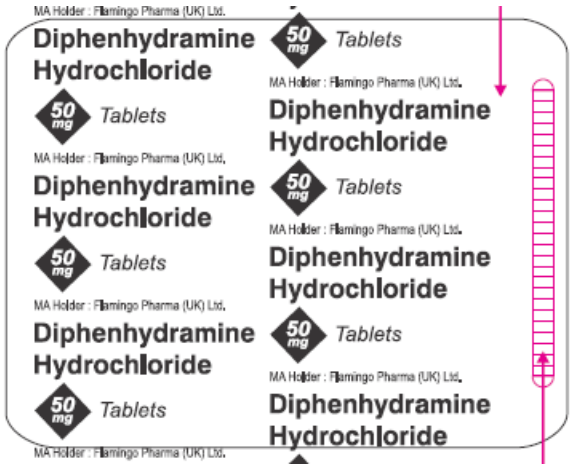

MA Holder : Flamingo Pharma (UK) Ltd.
Diphenhydramine Hydrochloride
50 mg Tablets

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.

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