IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific discussion

Paracetamol/Diphenhydramine Hydrochloride 500mg/25mg Film-coated Tablets
IE/H/462/1/DC, IE/H/463/1/DC & IE/H/464/1/DC

PARACETAMOL
And
DIPHENHYDRAMINE HYDROCHLORIDE

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Paracetamol/Diphenhydramine hydrochloride 500mg/25mg Film-coated tablets from Chanelle Medical on 6th January 2017 *for the short term treatment of bedtime symptoms of pain, for example arising from colds and flu, rheumatic and muscle pain, backache, toothache, headache and period pain which is causing difficulty in getting to sleep.*

The legal basis for the application is a generic application according to Article 10 (1) of Directive 2001/83/EC. This is an abridged application, no non-clinical or clinical studies have been undertaken in support of this application The RMS is IE, with AT, DE, IT, PL, PT, UK as CMS'.

The reference medicinal product is Panadol Night, authorised in Ireland on 18-9-1998, and the product licence number is PA 678/39/8. The Marketing Authorisation Holder (MAH) for the reference medicinal product is Glaxo Smith Kline Consumer Health Care (Ireland) Ltd.

This is a non-prescription medicine which may be supplied through pharmacies only.

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

Name of the product	Paracetamol/Diphenhydramine Hydrochloride 500mg/25mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	PARACETAMOL and DIPHENHYDRAMINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N02BE01 Analgesics & Antipyretics R06AA02 Aminoalkyl ethers
Pharmaceutical form and strength(s)	500mg/25mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA 688/037/001 PA 688/038/001 PA 688/039/001
Marketing Authorisation Holder	Chanelle Medical
MRP/DCP No.	IE/H/462/1/DC, IE/H/463/1/DC & IE/H/464/1/DC
Reference Member State	IE
Concerned Member State	IT UK PL AT DE PT

II QUALITY ASPECTS

II.1. Introduction

This application is for Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets.

II.2 Drug substance

The active substances are paracetamol and diphenhydramine hydrochloride, established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The medicinal product contains 500 mg of paracetamol and 25 mg of diphenhydramine hydrochloride.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the tablet dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of Paracetamol 500 mg/Diphenhydramine hydrochloride 25 mg. As Paracetamol 500 mg/Diphenhydramine hydrochloride 25 mg are widely used, well-known active substances, the applicant has not provided additional studies and none are required.

A non-clinical overview based on bibliographic references is provided. GLP standards cannot be established for these literature reference, however, this is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

A justification for the absence of specific study data in the environmental risk assessment was provided and the introduction of Paracetamol 500 mg/Diphenhydramine hydrochloride 25 mg to the market will not lead to an increase in environmental exposure.

III.6 Discussion on the non-clinical aspects

The use of Paracetamol 500 mg/Diphenhydramine hydrochloride 25 mg is well established. As Paracetamol 500 mg/Diphenhydramine hydrochloride 25 mg tablets are widely used, well-known active substances, the applicant has not provided additional non-clinical studies and further repetitive tests on animals are not required.

IV CLINICAL ASPECTS

IV.1 Introduction

Paracetamol is one of the most commonly used analgesic and antipyretic medicines around the world, available without a prescription, both in mono- and multi-component preparations

Diphenhydramine is a sedating antihistamine with antimuscarinic and pronounced sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema, rhinitis and conjunctivitis, and in pruritic skin disorders. Diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of antihistamine at the H1 receptor sites. However, like most H1 antihistamines it has additional sedative anticholinergic (muscarinic) and local anaesthetic properties. It is used for the symptomatic relief of allergic conditions. Diphenhydramine may be used as a hypnotic in the short-term management of insomnia due to its pronounced central sedative properties.

The legal basis for the application is a generic application according to Article 10 (1) of Directive 2001/83/EC. No clinical development programme has been conducted by the applicant. The application contains an adequate review of published clinical data. A bioequivalence study is not presented as the proposed product, is a well-established use product with an established safety profile. The brand leader has been on the market in Europe for more than 15 years. In addition the product complies with the Biopharmaceutical Classification System (BCS) - based biowaiver guidance as per Appendix III of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.

Both active substances have been authorised for long periods of time and the safety and efficacy profiles are well-characterised. Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets and Panadol Night tablets can be considered pharmaceutically equivalent.

The content of the SmPC approved during this decentralised procedure is in accordance with that accepted for the reference product Panadol Night with the addition of some updates.

IV.2 Pharmacokinetics

The Pharmacokinetics and pharmacodynamics of both paracetamol and diphenhydramine hydrochloride are well described and are adequately summarised in the clinical dossier.

Paracetamol
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration in plasma generally reaches a peak in 30-120 minutes; plasma half-life is 1-4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids. Plasma binding is variable. Paracetamol is extensively metabolized and only 2-5% of a therapeutic dose is excreted unchanged in the urine. Although biotransformation occurs predominately in the liver, there may be some metabolism of the drug in the gut and kidney. The major metabolites of paracetamol are the sulphate and glucuronide conjugates, but a minor fraction is converted by hepatic mixed function oxidase to a highly reactive alkylating metabolite. Excretion is almost exclusively renal in the form

Renal insufficiency
In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with renal failure (GFR≤50ml/min), to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.

Diphenhydramine Hydrochloride
Diphenhydramine is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations occur about 1 to 4 hours after oral doses. Diphenhydramine HCl belongs to BCS-Class I (high solubility and high permeability). Absorption- related drug interactions are less likely in Class 1 drugs, however, increasingly the contribution of the intestinal mucosa to first-pass metabolism is being recognized. Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Diphenhydramine is metabolized by the hepatic cytochrome P-450 enzyme system, therefore, the increased serum-elimination half-life values, slower clearance rates, and a trend towards decreased volumes of distribution with increasing age might be expected. Age-related decreases in hepatic function, including decreased liver blood flow, smaller liver size and diminished number and metabolizing capacity of hepatocytes have been well documented in geriatric populations.

Conclusion:
Paracetamol has excellent oral bioavailability; peak plasma concentrations occur within 30-120 minutes after oral ingestion, and 90-100% of the drug may be recovered in the urine.

Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations occur about 1 to 4 hours after oral doses. Diphenhydramine is widely distributed throughout the body including the CNS.

IV.3 Pharmacodynamics

The pharmacodynamics of paracetamol and diphenhydramine hydrochloride have been adequately discussed by the applicant and has been based on published literature.

Paracetamol
Paracetamol has analgesic and antipyretic effects. It is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its ability to reduce fever (a central action) and to induce analgesia.

Diphenydramine Hydrochloride
Diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of antihistamine at the H1 receptor sites. However, like most H1 antihistamines it has additional sedative anticholinergic (muscarinic) and local anaesthetic properties.

IV.4 Clinical Efficacy

The efficacy of paracetamol and diphenhydramine hydrochloride and in the indications proposed are well established and have been adequately described by the applicant.

SmPC changes:

The indication:
"*for the short term treatment of bedtime symptoms of pain, for example arising from colds and flu, rheumatic and muscle pain, backache, toothache, headache and period pain which is causing difficulty in getting to sleep"*

The indication remains almost fully in line with the indication of the reference medicinal product but has been slightly

reworded to clarify the symptoms and the action of diphenhydramine hydrochloride.

The posology:

Adults (including the elderly) and adolescents 16 years and over:
2 tablets to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4000 mg (including this product) in any 24 hour period. Allow at least four hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets:
Two tablets (1000mg paracetamol, 50mg diphenhydramine) in 24 hours.

Adolescents 12 to 15 years:
1 tablet to be taken 20 minutes before bedtime. Other products containing paracetamol may be taken during the day but
the total daily dose of paracetamol must not exceed 3000 mg (including this product) in any 24 hour period.
Allow at least four to six hours between taking any paracetamol-containing product and this product.
Maximum daily dose of Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets:
One tablet (500mg paracetamol, 25mg diphenhydramine) in 24 hours.

Background:
The recommended maximum daily dose (MDD) of paracetamol is 4g for adults and adolescents over 16y.

The recommended MDD of paracetamol is 3g for children and adolescents 12y to 15y, this is in line with Ireland's recommendations for liquid paracetamol formulations for this age group. The maximum posology of paracetamol for the 12 to 15 year age group is 750mg of at any one time, therefore the recommended posology for Paracetamol/Diphenhydramine Hydrochloride 500 mg/25mg Film-coated Tablets for this age group is:
"1 tablet to be taken 20 minutes before bedtime"

For specific situations the MDD of paracetamol should not exceed 2g (please see the SmPC for details)

IV.5 Clinical Safety

The safety data provided by the applicant is based on literature review. The safety profile of paracetamol and diphenhydramine hydrochloride are well known both as monotherapies and in combination together. The applicant has given an adequate overview of the safety of paracetamol and diphenhydramine hydrochloride. The Summary of Product Characteristics (SmPC) and Patient Leaflet (PL) contain the relevant contraindications, safety warnings and have been updated in line with the reference medicinal product and current data relating to the active substances.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan

The applicant 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 Paracetamol/Diphenhydramine Hydrochloride. The revised RMP (version 1.2 dated final sign off 16/8/2016) is acceptable. Routine risk minimization activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

- Summary table of safety concerns as approved in RMP

Important identified risks	1. Hypersensitivity 2. Hepatotoxicity 3. Use in renal impairment 4. Use with alcohol 5. Anticholinergic effects, particularly in the elderly 6. Sedation 7. Interaction with anticoagulants 8. Interaction with domperidone, metoclopramide and cholestyramine 9. Interactions with MAOIs, drugs with antimuscarinic properties, antihistamine containing preparations, enzyme inducers and inhibitors 10. QT prolongation
Important potential risks	Overdose Drug abuse
Missing information	Use in pregnancy and breastfeeding Use in children under 12 years

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date
Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects

The legal basis for the application is a generic application according to Article 10 (1) of Directive 2001/83/EC. No clinical studies were submitted with this generic application nor has a bioequivalence study been performed and this has been satisfactorily justified. The submitted clinical documentation is being based on data available in published literature. Paracetamol/Diphenhydramine hydrochloride 500mg/25mg Film-coated tablets is a well-established use product with an established safety profile. The product complies with the BCS- based Biowaiver guidance as per Appendix III of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. Both active substances have been authorised for long periods of time and the safety and efficacy profiles are well-characterised. Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets and Panadol Night tablets can be considered pharmaceutically equivalent.

The proposed product information (SmPC and PL) has been updated in accordance with the innovator’s product information and with current information pertinent to the active substances.

V OVERALL CONCLUSIONS

Paracetamol/Diphenhydramine hydrochloride 500mg/25mg Film-coated tablets is a generic form of Panadol Night (PA 678/39/8) authorised in Ireland on 18-9-1998. Panadol Night, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile. Both active substances have been authorised for long periods of time and the safety and efficacy profiles are well-characterised. Paracetamol/Diphenhydramine Hydrochloride 500 mg/25 mg Film-coated Tablets and Panadol Night tablets can be considered pharmaceutically equivalent.

The SmPC is consistent with that of the reference product and has been updated with current information pertinent to the active substances.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Paracetamol/Diphenhydramine hydrochloride 500mg/25mg Film-coated tablets is pharmaceutically equivalent to the reference product and has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.