IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Zopiclone Pinewood 7.5 mg Film-Coated Tablets
Zopiclone
PA0281/257/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Zopiclone Pinewood 7.5 mg Film-Coated Tablets, from Pinewood Laboratories Ltd on 8th July 2022 for the short-term treatment of insomnia in adults.

The marketing authorisation application was submitted via the Decentralised Procedure (DCP), with Ireland as Reference Member State (RMS). The application was submitted in accordance with Article 10(1) of Directive 2001/83/EC. The EU reference medicinal product, selected in support of this generic application, is Imovane 7.5 mg Film-coated tablets (9514) by Sanofi Oy, registered since 22/07/1987 in Finland. The applicant demonstrated essential similarity to the reference medicinal product by submission of one fasted single-dose bioequivalence study (Study 17-VIN-0138) assessing the bioequivalence between Imovane 7.5 mg and Zopiclone Pinewood 7.5 mg tablets.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.
Zopiclone Pinewood 7.5 mg Tablet contains zopiclone, a non-benzodiazepine hypnotic agent used in the short-term treatment of insomnia in adults, and is granted a marketing authorisation as a medicinal product that is subject to prescription only, which may not be renewed.

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	Zopiclone Pinewood 7.5 mg Film-CoatedTablets
Name(s) of the active substance(s) (INN)	Zopiclone
Pharmacotherapeutic classification (ATC code)	N05CF01
Pharmaceutical form and strength(s)	7.5 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/257/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd.
MRP/DCP No.	IE/H/1190/001/DC
Reference Member State	IE
Concerned Member State	

II. QUALITY ASPECTS

II.1. Introduction

This application is for Zopiclone Pinewood 7.5 mg Film-Coated Tablets.

II.2 Drug substance

The active substance is zopiclone, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is 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 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.

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 tablets 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 Ph. Eur./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 Zopiclone Pinewood 7.5 mg Film-Coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Imovane 7.5 mg Film-coated tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Zopiclone Pinewood is a generic product, it will not lead to an increased exposure to the environment. A justification for the absence of ERA studies was provided and is acceptable.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of zopiclone are well known. As zopiclone is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Zopiclone is a well known active substance with established efficacy and tolerability.

The indication and posology approved for Zopiclone Pinewood 7.5 mg Film-Coated Tablets are in line with the reference medicinal product Imovane 7.5 mg Film-coated tablets (9514) by Sanofi Oy.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product, Zopiclone Pinewood 7.5 mg Film-Coated Tablets, is compared with the pharmacokinetic profile of the reference product, Imovane 7.5 mg Film-coated tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Zopiclone Tablets BP 7.5 mg (Zopiclone Pinewood 7.5 mg Film-Coated Tablets) manufactured by Ipca Laboratories Limited, Athal, India, was compared to the reference product Imovane 7.5 mg film coated tablets of Sanofi Ltd, Huopalahdentie 24, 00350 Helsinki, Finland. Based on the pharmacokinetic parameters of active substance, the reference tablet Zopiclone Tablets BP 7.5 mg (Ipca Laboratories Limited, India) and test tablet Imovane 7.5 mg film coated tablets (Sanofi Ltd, Finland) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

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 zopiclone.

- *Risk Management Plan (usual pharmacovigilance requirements and/or additional requirements)*
- *The proposed schedule for submission of PSURs should be addressed.*

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

Study 17-VIN-0138:
An open label, randomised, two treatment, two period, two sequence, two way crossover, single dose oral bioequivalence study of Zopiclone Tablets BP 7.5 mg (Ipca Laboratories Limited, India) and Imovane 7.5 mg film-coated tablets (Sanofi Ltd, Finland) in healthy, adult, human subjects under fasting condition.

After overnight fasting of at least 8 hours, subjects were administered a single dose of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 12 days, which was sufficient to eliminate any carryover effect of the drug between treatment periods.

Summary statistics for the pharmacokinetic parameters for zopiclone, between the test and reference medicinal products, are presented below.

Table 1: Geometric mean and 90% CI for Zopiclone

Parameters	Geometric Least Square Mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-t} (ng.hr/mL)	545.158	529.073	103.04	100.66	105.48
C_{max} (ng/mL)	77.546	71.766	108.05	101.97	114.51

C_{max} = maximum plasma concentration
AUC_{0-t} = area under the plasma concentration-time curve from zero to t hours

The 90% confidence intervals of the test/reference ratio for AUC_{0-t} and C_{max} values for zopiclone lie within the acceptable limits of 80.00 % to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's (Pinewood) test product, Zopiclone Tablets BP 7.5 mg (Ipca Laboratories Limited, India) is bioequivalent to the reference product, Imovane 7.5 mg film coated tablets (Sanofi Ltd, Finland).

IV.3 Pharmacodynamics

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

IV.4 Clinical Efficacy

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

IV.5 Clinical Safety

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

Risk Management Plan

The submitted Risk Management Plan, version 0.4, signed 23/12/2021 is considered acceptable.

No safety concerns were proposed by the applicant, which is endorsed.

Routine pharmacovigilance and risk minimization activities were proposed by the applicant, which is endorsed.

Periodic Safety Update Reports (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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Zopiclone Pinewood 7.5 mg Film-Coated Tablets is a generic form of Imovane 7.5 mg Film-coated tablets (Sanofi Oy, Finland). Imovane 7.5 mg Film-coated tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

No new non-clinical or clinical safety concerns have been identified for Zopiclone Pinewood 7.5 mg Film-Coated Tablets. Other than the single bioequivalence study, no new clinical efficacy or safety data were submitted as part of this application, and none are required for an application of this type. Extensive clinical experience with zopiclone is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and its benefit/risk balance is considered similar.

V. OVERALL CONCLUSIONS

Zopiclone Pinewood 7.5 mg Film-Coated Tablets is a generic form of Imovane 7.5 mg Film-coated tablets (Sanofi Oy, Finland). Imovane 7.5 mg Film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents.

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

No safety concerns were proposed. Routine pharmacovigilance and risk minimization activities are considered appropriate.

The HPRA, on the basis of the data submitted considered that Zopiclone Pinewood 7.5 mg Film-Coated Tablets demonstrated bioequivalence with the reference product as well as a satisfactory benefit/risk profile and therefore granted a marketing authorisation.

VI. REVISION DATE

08.06.2027