IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Zolpidem Tartrate 5 mg Film-coated Tablets
ZOLPIDEM TARTRATE
PA23176/003/001

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/6325/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 24th September 2019 under procedure number IE/H/1051/001-002/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0343/005/001-002
Marketing Authorisation Holder: Key Pharmaceuticals Ltd

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 Medicines and Healthcare products Regulatory Agency (MHRA) granted Key Pharmaceuticals Ltd, marketing authorisations for the medicinal product Zolpidem Tartrate Tablets (PL 34424/0009-10; UK/H/6325/001-2/DC). The products are prescription-only medicine (POM) indicated for the short-term treatment of insomnia in adults where the insomnia is debilitating or is causing severe distress for the patient.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Stilnoct 5mg and 10mg Film-Coated Tablets which were first authorised to Lorex Synthélabo Limited on 16 December 1993 (Stilnoct 5mg Film-Coated Tablets; PL 04969/0017) and 16 September 1996 (Stilnoct 10mg Film-Coated Tablets; PL 04969/0027).
The reference products (PL 04969/0017 & 0027) subsequently underwent several changes of ownership procedures, the most recent of which was to Aventis Pharma Limited, UK on 03 December 2009 (Stilnoct 5mg Film-Coated Tablets; PL 04425/0618) and 26 January 2009 (Stilnoct 10mg Film-Coated Tablets; PL 04425/0619).

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

One bioequivalence study (conducted under fasting conditions) was submitted to support these applications. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

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.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 14 March 2017. After a subsequent national phase, a licence was granted in the UK on 29 March 2017.

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 5 mg or 10 mg zolpidem tartrate as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Tablet core:
Lactose monohydrate, microcrystalline cellulose PH101, sodium starch glycolate (Type A), hypromellose (HPMC E5) and magnesium stearate.

Film-coating:
Hypromellose (HPMC E3), macrogol (PEG-400) and titanium dioxide (E171).

Both strengths of the finished product are packed into :

- Aluminium (Al)/polyvinyl chloride (PVC) blisters in pack sizes of 28 film-coated tablets.
- High density polyethylene (HDPE) tablet containers with a child-resistant polypropylene cap containing 400 tablets.

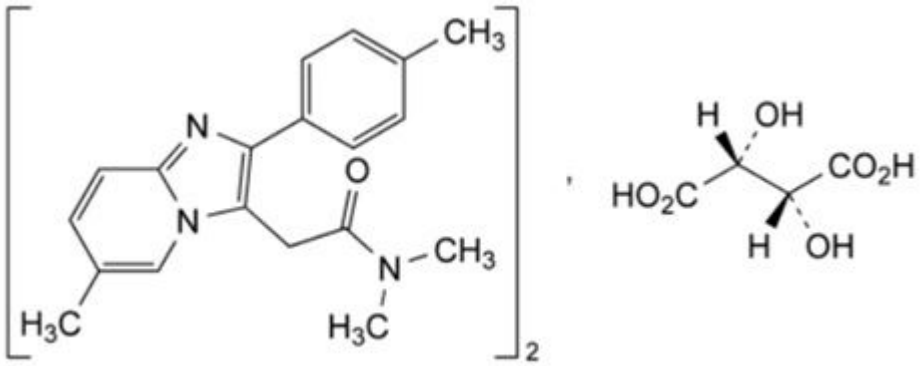
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Zolpidem tartrate
Chemical name: Bis[*N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Structural formula:



Molecular formula: $C_{42}H_{48}N_6O_8$
Molecular mass: 765 g/mol
Appearance: White or almost white, hygroscopic, crystalline powder.
Solubility: Slightly soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

Zolpidem tartrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, zolpidem tartrate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 5 mg or 10 mg zolpidem tartrate per tablet, that are generic versions of the reference products Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

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

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing processes have been validated at pilot scale batch sizes and have shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches and a satisfactory validation protocol has been provided.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years 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 these applications from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of zolpidem tartrate 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 Zolpidem Tartrate Tablets are 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
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of zolpidem tartrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 zolpidem tartrate.

Based on the data provided, Zolpidem Tartrate Tablets can be considered bioequivalent to Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

STUDY 1

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, oral, bioequivalence study of the applicant's test product Zolpidem 10mg Tartrate Tablets (Key Pharmaceuticals Ltd, UK) versus the reference productStilnoct 10mg Film-Coated Tablets (Aventis Pharma Limited, UK) in healthy, adult, subjects under fed conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 10 mg tablet) 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 16 hours after each administration. The washout period between the treatment phases was 11 days. The pharmacokinetic results are presented below:

Table: Summary statistics for the pharmacokinetic parameters for zolpidem is presented below:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$\ln C_{max}$	201.288	205.156	98.1	92.83 - 103.70	17.8	100.0
$\ln AUC_{0-t}$	738.494	722.798	102.2	96.49 - 108.18	18.4	100.0
$\ln AUC_{0-\infty}$	758.998	743.911	102.0	96.22 - 108.18	18.9	100.0

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

Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for zolpidem 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 test product is bioequivalent to the reference product Stilnoct 10mg Film-Coated Tablets (Aventis Pharma Limited, UK).

As the 5 mg and 10 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg strength tablet.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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 Zolpidem Tartrate Tablets.

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

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• hypersensitivity to active substance or other ingredients of the medicine • Acute and/or severe respiratory depression (breathing difficulties or slower breathing) • Next morning residual effect (Next-day psychomotor impairment) • Tolerance • Dependence • Rebound insomnia (rebound effect) • Amnesia (poor memory) • Psychiatric and abnormal reactions • Somnambulism (sleep walking) and associated behaviour • Additive effect of zolpidem due to interaction between zolpidem and other depressants of the central nervous system • Drug-drug interactions • Overdose • Abuse • Use in elderly (use in patient more than 65 years of age) • Use in patients with impaired hepatic function (liver problems) • Hallucinations, agitations and nightmares • Worsening of pre-existing depression.
Important potential risks	There are no important potential risks with zolpidem tartrate.
Missing information	• Use in children • Use during pregnancy. • Use during the breastfeeding / nursing • Fertility

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

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

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 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.

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. Extensive clinical experience with zolpidem tartrate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risk-benefit balance is considered similar and positive.

VI. REVISION DATE

May 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/6325/001-002/DC to IE/H/1051/001-002/DC	N/A	N/A	N/A	Approved 24/09/2019
MA Transfer	CRN00C5DD	SmPC Section 7, 8, 10 Leaflet New MA Holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/003/001-002	23/04/2021	23/04/2021	Approved