Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Zolpidem Tartrate 5mg Film-coated Tablets
Zolpidem Tartrate 10mg Film-coated Tablets

(Zolpidem tartrate)

Procedure No: UK/H/6325/001-2/DC

UK Licence Number: PL 34424/0009-10

Key Pharmaceuticals Ltd.

LAY SUMMARY

Zolpidem Tartrate 5mg Film-coated Tablets
Zolpidem Tartrate 10mg Film-coated Tablets

This is a summary of the Public Assessment Report (PAR) for Zolpidem Tartrate 5mg Film-coated Tablets (PL 34424/0009; UK/H/6325/001/DC) and Zolpidem Tartrate 10mg Film-coated Tablets (PL 34424/0010; UK/H/6325/002/DC). It explains how Zolpidem Tartrate 5mg and 10 mg Film-coated Tablets 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 Zolpidem Tartrate 5mg and 10 mg Film-coated Tablets.

The products will be collectively referred to as Zolpidem Tartrate Tablets throughout the remainder of this public assessment report (PAR).

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

What are Zolpidem Tartrate Tablets and what are they used for?
Zolpidem Tartrate Tablets is a 'generic medicine'. This means that Zolpidem Tartrate Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK).

This medicine is used for temporary sleep problems **in adults** that are causing them severe distress or that are affecting their everyday life. This includes sleep problems **in adults** such as:

- Difficulty falling asleep
- Waking in the middle of the night
- Waking too early

The patient's doctor will identify their sleep problem wherever possible and the underlying factors before prescribing Zolpidem Tartrate Tablets for the patient.

The failure of the patient's sleep problems to stop after a 7-14 day course of treatment may indicate they have an underlying disorder, the patient's doctor will assess them at regular intervals.

Zolpidem Tartrate Tablets are **not** meant to be used every day for long periods of time. The patient should ask their doctor for advice if they are unsure.

How does Zolpidem Tartrate Tablets work?
Zolpidem Tartrate Tablets contain an active substance called zolpidem tartrate. This belongs to a group of medicines called hypnotics. It works by acting on the brain to help the patient sleep.

How are Zolpidem Tartrate Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Taking Zolpidem Tartrate Tablets

- Take Zolpidem Tartrate Tablets by mouth.
- Swallow the tablet whole with a drink of water.
- The 10 mg tablet can be divided into equal doses.

- The recommended dose per 24 hours is 10 mg. A lower dose may be prescribed to some patients.
- Zolpidem Tartrate Tablets should be taken as a single intake, just before bedtime.
- The patient must make sure they have a period of at least 8 hours after taking Zolpidem Tartrate Tablets before performing activities that require their alertness.
- Do not exceed 10 mg per 24 hours.
- The usual length of treatment is 2 days to 4 weeks.

Adults
The usual dose is one 10 mg Zolpidem Tartrate Tablet (or two 5 mg Zolpidem Tartrate Tablets) just before bedtime.

Elderly
The usual dose is one 5 mg Zolpidem Tartrate Tablet just before bedtime.

Patients with liver problems
The usual starting dose is one 5 mg Zolpidem Tartrate Tablet just before bedtime. The patient's doctor may decide to increase this to one 10 mg Zolpidem Tartrate Tablet (or two 5 mg Zolpidem Tartrate Tablets) if it is safe to do so.

Children and Adolescents
Zolpidem Tartrate Tablets should not be used in people under 18 years old.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Zolpidem Tartrate Tablets is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Zolpidem Tartrate Tablets have been shown in studies?
Because Zolpidem Tartrate Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines, Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Zolpidem Tartrate Tablets?
Because Zolpidem Tartrate Tablets are generic medicines and are bioequivalent to the reference medicines Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK), their possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Zolpidem Tartrate Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Zolpidem Tartrate Tablets approved?
It was concluded that, in accordance with EU requirements, Zolpidem Tartrate Tablets have been shown to have comparable quality and to be bioequivalent to Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK). Therefore, the MHRA decided that, as for Stilnoct 5mg and 10mg Film-Coated Tablets (Aventis Pharma Limited, UK); the benefits are greater than the risks and recommended

that Zolpidem Tartrate Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Zolpidem Tartrate Tablets?
A risk management plan (RMP) has been developed to ensure that Zolpidem Tartrate Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Zolpidem Tartrate Tablets 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 and healthcare professionals will be monitored and reviewed continuously.

Other information about Zolpidem Tartrate Tablets
Agreement for granting Marketing Authorisations was given on 14 March 2017 by the UK and EU member state Ireland.

Marketing Authorisations were granted in the UK on 29 March 2017.

The full PAR for Zolpidem Tartrate Tablets follows this summary.

For more information about treatment with Zolpidem Tartrate Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2017.

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I INTRODUCTION

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 products, 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.

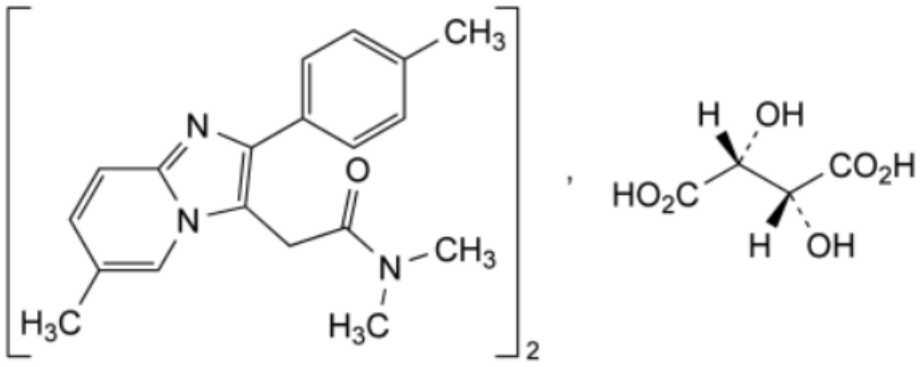
Not all pack sizes may be marketed.

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 products, 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 products 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

An open-label, balanced, randomised, single oral dose, two-treatment, two-sequence, two-period, crossover, bioequivalence study of the applicant's test product Zolpidem 10mg Tartrate Tablets (Key Pharmaceuticals Ltd, UK) versus the reference product Stilnoct 10mg Film-Coated Tablets (Aventis Pharma Limited, UK) in healthy, adult, subjects under fasting 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)%			
lnC_{max}	201.288	205.156	98.1	92.83 - 103.70	17.8	100.0
$lnAUC_{0-t}$	738.494	722.798	102.2	96.49 - 108.18	18.4	100.0
$lnAUC_{0-\infty}$	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 strength test product meets 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 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.

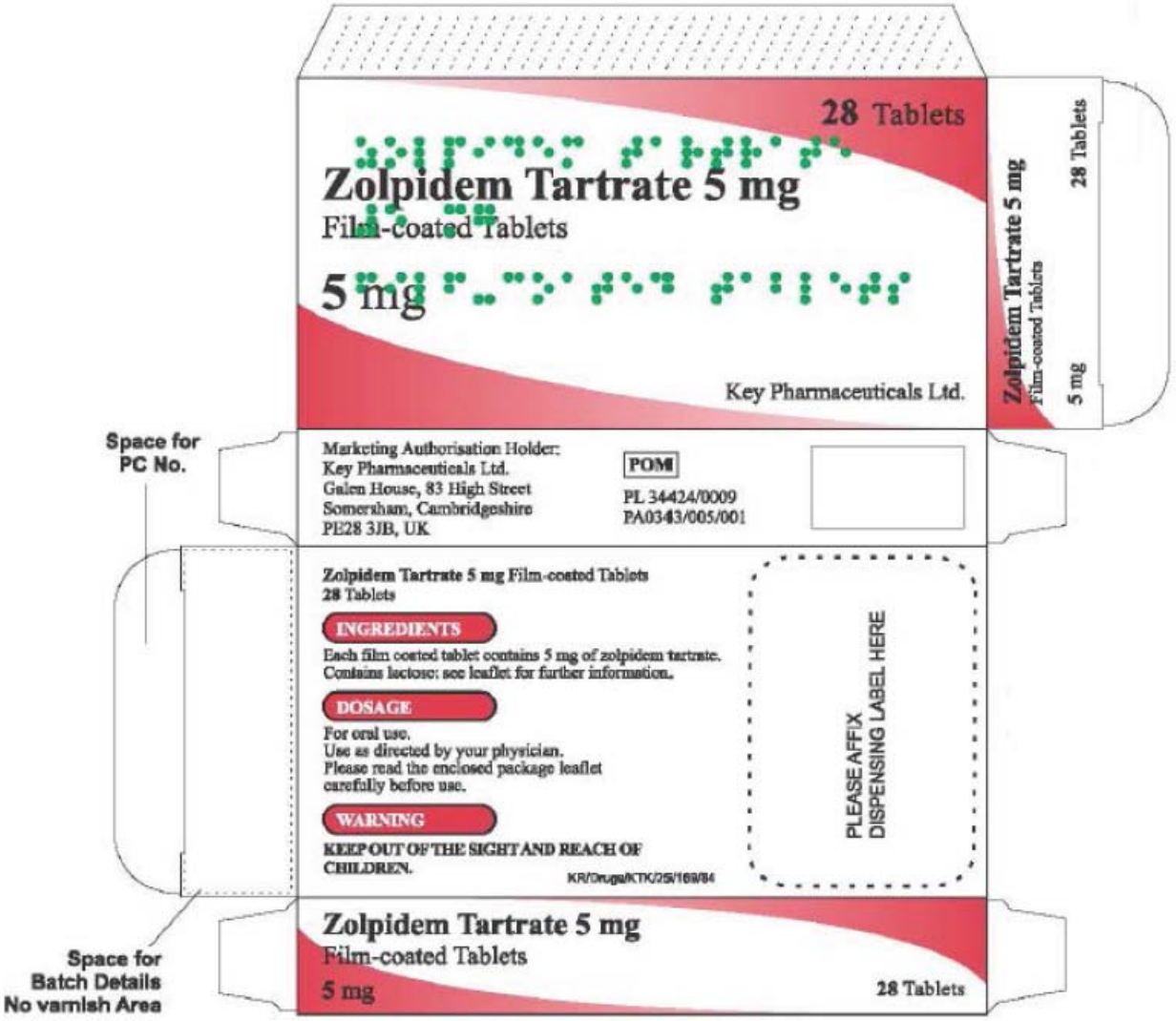
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

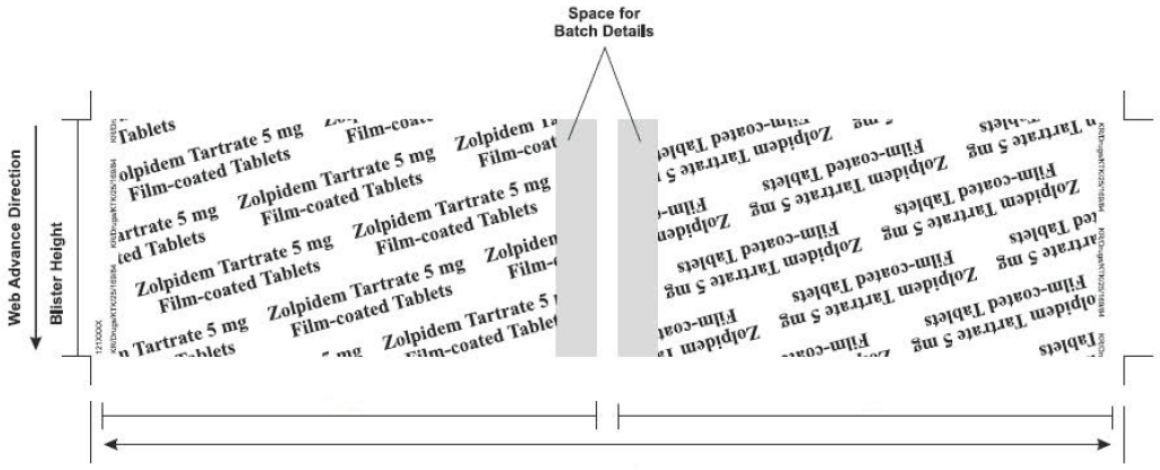
VI Overall conclusion, benefit/risk assessment and recommendation

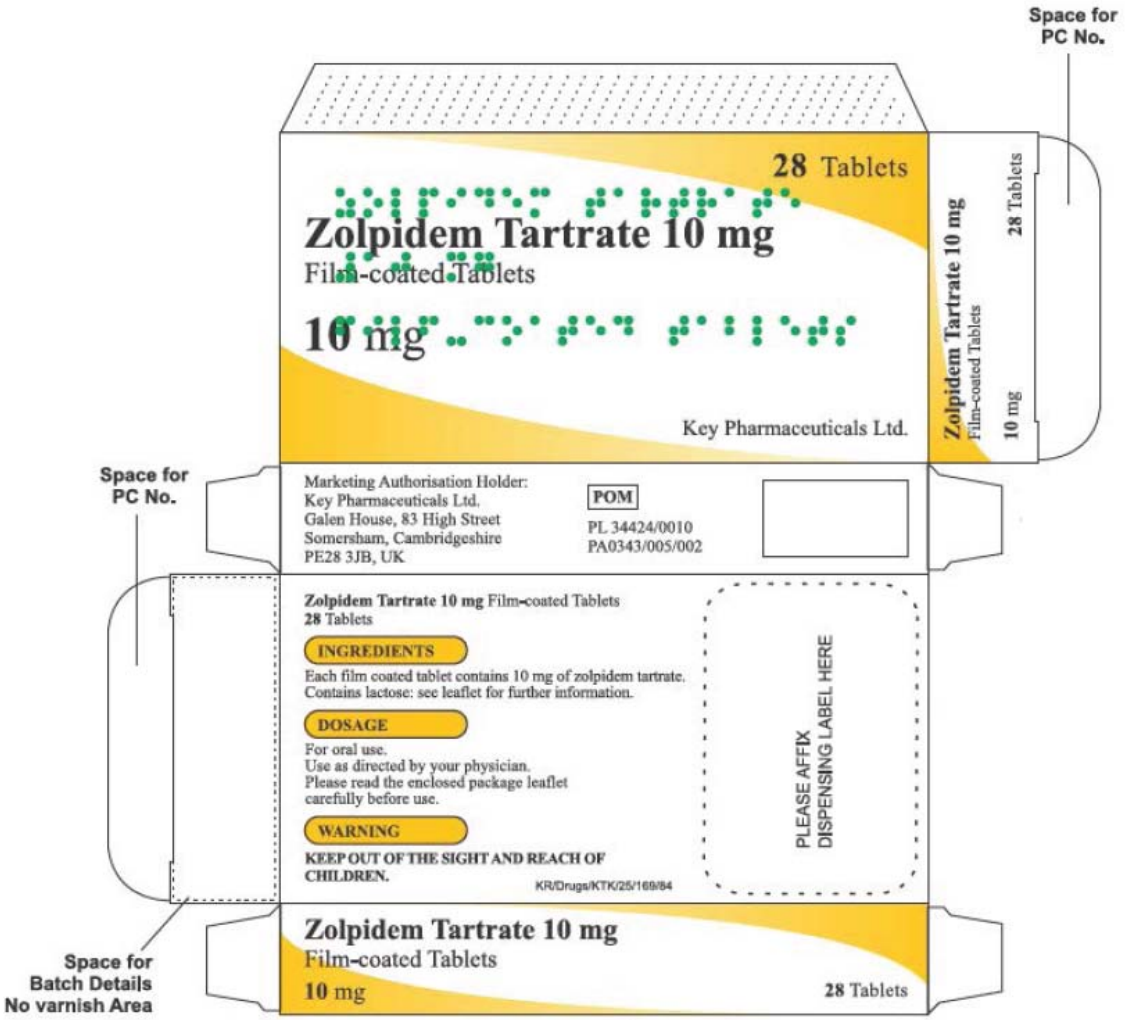
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with zolpidem tartrate is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risk-benefit balance is considered similar and positive.

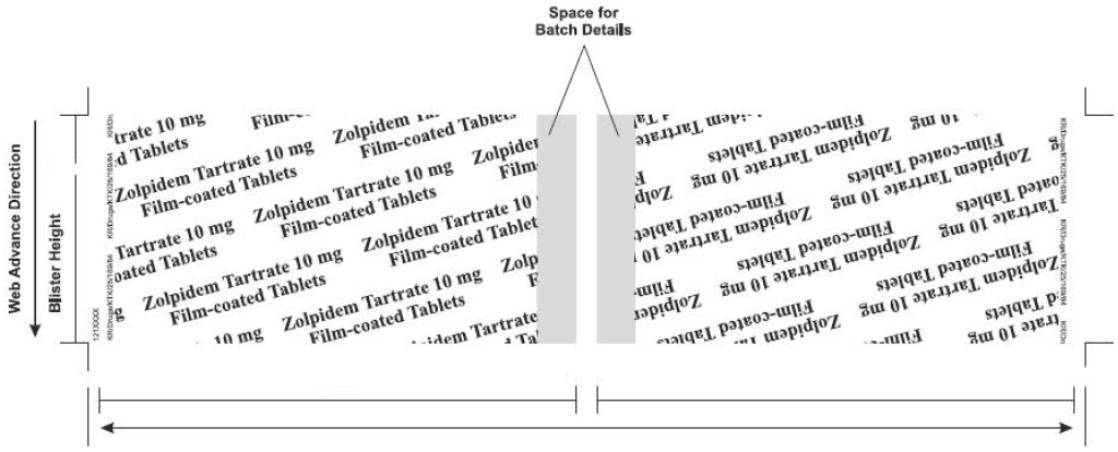
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Zolpidem Tartrate Tablets is presented below:






Space for PC No.
28 Tablets
Zolpidem Tartrate 10 mg
Film-coated Tablets
10 mg
Key Pharmaceuticals Ltd.
Zolpidem Tartrate 10 mg
Film-coated Tablets
28 Tablets
10 mg
Space for PC No.
Marketing Authorisation Holder:
Key Pharmaceuticals Ltd.
Galen House, 83 High Street
Somersham, Cambridgeshire
PE28 3JB, UK
POM
PL 34424/0010
PA0343/005/002
Zolpidem Tartrate 10 mg Film-coated Tablets
28 Tablets
INGREDIENTS
Each film coated tablet contains 10 mg of zolpidem tartrate.
Contains lactose: see leaflet for further information.
DOSAGE
For oral use.
Use as directed by your physician.
Please read the enclosed package leaflet carefully before use.
WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
KR/Drugs/KTK/25/169/84
PLEASE AFFIX DISPENSING LABEL HERE
Space for Batch Details No varnish Area
Zolpidem Tartrate 10 mg
Film-coated Tablets
10 mg
28 Tablets


Space for Batch Details
Web Advance Direction
Blister Height
Zolpidem Tartrate 10 mg
Film-coated Tablets

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
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