Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Zopiclone 7.5 mg film-coated tablets

(Zopiclone)

UK Licence No: PL 20416/0551

Crescent Pharma Limited

LAY SUMMARY
Zopiclone 7.5 mg film-coated tablets
(Zopiclone)

This is a summary of the Public Assessment Report (PAR) for Zopiclone 7.5 mg film-coated tablets (PL 20416/0551). For ease of reading, this medicinal product will be referred to as Zopiclone Tablets in this Lay Summary.

This summary explains how Zopiclone Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

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

What are Zopiclone Tablets and what are they used for?
This medicine is the same as Zopiclone 7.5mg film-coated tablets (PL 19156/0076; Jubilant Pharmaceuticals NV), which is already authorised in the UK. The licence holder (Jubilant Pharmaceuticals NV) for Zopiclone 7.5mg film-coated tablets (PL 19156/0076) has agreed that its own scientific data can be used as a basis for the grant of identical licence for Zopiclone 7.5 mg film-coated tablets (PL 20416/0551).

Zopiclone tablets are used in adults for the short-term treatment of sleeplessness which causes patients extreme distress. The treatment can take a few days to 2 weeks and usually does not take longer than 4 weeks.

How do Zopiclone Tablets work?
Zopiclone tablets are a sedative-hypnotic drug with zopiclone as active ingredient. Zopiclone tablets induces sleep and helps the patient to relax.

How are Zopiclone Tablets used?
Zopiclone Tablets are taken orally. The tablets should be swallowed whole without sucking or chewing. Zopiclone Tablets should be taken before bedtime.

The tablets can be divided into equal doses:
- lay the tablet on a desk,
- take the left and right thumb or forefinger and press on both sides of the scoring line.

Patients must not use more than one tablet per day.

Elderly and patients with impaired liver or kidney function or severe respiratory failure (a condition in which the gas exchange in the lungs is insufficient to meet the body's needs) should start the treatment with half a tablet per day.

Zopiclone tablets should not be used in children and adolescents less than 18 years. The safety and efficacy of Zopiclone tablets in children and adolescents aged less than 18 years have not been established.

This medicine can only be obtained with a prescription.

For further information on how Zopiclone Tablets are used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Zopiclone Tablets have been shown in studies?
As Zopiclone Tablets (PL 20416/0551) is considered to be identical to the cross-reffered product, Zopiclone 7.5mg film-coated tablets (PL 19156/0076), their benefits and risks are taken as being the same as those for the cross-referred product.

What are the possible side effects from Zopiclone Tablets?
Like all medicines, Zopiclone Tablets can cause side effects, although not everybody gets them.

The most commonly reported adverse effects are: sleepiness during the day, a bitter taste, a dry mouth and a reduced alertness. These affect 1 to 10 users in 100.

For the full list of all side effects reported with Zopiclone Tablets, see section 4 of the package leaflet.

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

Why are Zopiclone Tablets approved?
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Zopiclone Tablets outweigh the risks, and the grant of a Marketing Authorisation was recommended.

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

Other information about Zopiclone Tablets
A Marketing Authorisation was granted in the UK on 20 August 2018.

The full PAR for Zopiclone Tablets follows this summary.

This summary was last updated in October 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Crescent Pharma Limited a Marketing Authorisation for the medicinal product Zopiclone 7.5 mg film-coated tablets (PL 20416/0551) on 20 August 2018

This is a prescription only medicine (POM), used for the short-term treatment of insomnia in adults. Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Zopiclone 7.5mg film-coated tablets (PL 19156/0076), which was originally authorised to Jubilant Pharmaceuticals NV (PL 19156/0076) on 16 October 2013.

Zopiclone is a benzodiazepine-like hypnotic agent which belongs to the group of cyclopyrrolones (a group of medicines that are not chemically related to barbiturates, benzodiazepines, or other known hypnotics). The pharmacological properties are: sedation, anxiolysis, anticonvulsion, muscle relaxation. These effects are related to its high affinity and specific agonist action at central receptors belonging to the 'GABA' macromolecular receptor complex modulating the opening of the chloride ion channel. However, it has been shown that zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines including different conformational changes in the receptor complex.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product. The applicant cross-refers to the data for Zopiclone 7.5mg film-coated tablets (PL 19156/0076), to which this application is claimed to be identical. The applicant has included expert reports of the application. Signed declarations and copies of the experts' CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

The MHRA 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 and assembly of this product.

II QUALITY ASPECTS

II.1 Introduction

This is a simple (informed consent) application for Zopiclone 7.5 mg film-coated tablets (PL 20416/0551), submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Zopiclone 7.5mg film-coated tablets (PL 19156/0076), which was originally authorised to Jubilant Pharmaceuticals NV (PL 19156/0076) on 16 October 2013. The current application is considered valid.

II.2. Drug Substance

Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3. Medicinal Product

Name

The proposed product name is Zopiclone 7.5 mg film-coated tablets. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size

Each film-coated tablet contains 7.5 mg zopiclone, as active ingredient. The route of administration is oral.

The finished products are packed in polyvinylchloride (PVC)/ polyvinylidenechloride (PVDC)/Al blisters with a pack size of 28 film-coated tablets.

The proposed shelf-life is 3 years with a special storage condition “Do not store above 25ºC”.

The proposed packaging, shelf-life and storage condition are consistent with the details registered for the cross-reference product.

Marketing Authorisation Holder/Contact Persons/Company

Crescent Pharma Limited, Units 3 & 4, Quidhampton Business Units, Polhampton Lane, Overton, Hampshire RG25 3ED, United Kingdom

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory *Curriculum Vitae* (CV) has been provided.

Manufacturer

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification

The proposed finished product specifications are in line with the details registered for the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The quality data for this application is consistent with those approved for Zopiclone 7.5mg film-coated tablets (PL 19156/0076) and, as such, have been judged to be satisfactory. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

A suitable justification has been provided for not submitting an environmental risk assessment.

The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Bioequivalence

No bioequivalence data are required to support this simple abridged application as the proposed product are manufactured to the same formula utilising the same process as the cross-reference product, Zopiclone 7.5mg film-coated tablets (PL 19156/0076).

Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) 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 Zopiclone 7.5 mg film-coated tablets.

A summary of safety concerns as approved in the RMP, is listed below:

Summary of safety concerns	
Important identified risks	• Respiratory depression • Anterograde amnesia • Psychiatric and paradoxical reactions • Tolerance and dependence • Withdrawal symptoms/insomnia • Hypersensitivity and severe skin disorders
Important potential risks	• Abuse and diversion • Risk of fall in the elderly • Use in patients with severe hepatic insufficiency • Neonatal effects of 3rd trimester/labour exposure
Missing information	• Use during pregnancy and lactation • Use in paediatric population • Use in patients with renal insufficiency • Dose adjustments in concomitant use with CYP3A4 inhibitors/inducers

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V User consultation

A bridging report has been provided divided in to two parts: a) bridging of the text (content) with the leaflet of the cross-reference product Zopiclone 7.5mg film-coated tablets (Jubilant Pharmaceuticals NV) and b) bridging of readability (layout, design) with the leaflet of Cetirizine Dihydrochloride 10mg film-coated tablets (Crescent Pharma).

The first bridging report (a) has not been assessed as the proposed text identical to that of the cross-referenced product. The layout and design (two columns, bold heading, font size) is similar to that shown for the user tested Cetirizine Dihydrochloride 10mg film-coated tablets (Crescent Pharma). On this basis the readability of the proposed leaflet mock-up is accepted.

VI Overall conclusion, benefit/risk assessment and recommendation

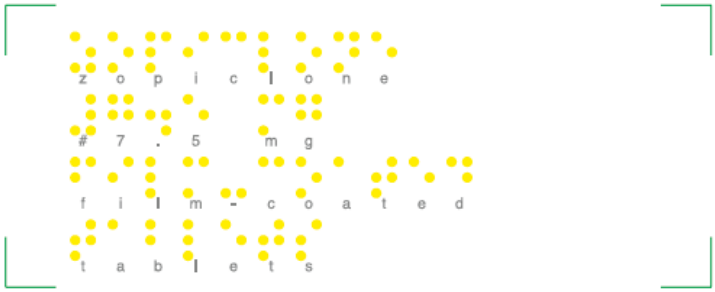
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with zopiclone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

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

The approved labelling for Zopiclone 7.5 mg film-coated tablets is presented below:

BRAILLE


Zopiclone
Film-coated tablets
7.5mg
Each film-coated tablet contains 7.5mg zopiclone.
Also contains lactose monohydrate
(see leaflet for further information).
28 Film-coated tablets
Crescent
PHARMA LIMITED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Crescent Pharma Ltd.
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitmen

Date submitted	Application type	Scope	Outcome