LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zopiclone Orion
(zopiclone)

SE/H/1581/01-02/DC

This module reflects the scientific discussion for the approval of Zopiclone Orion. The procedure was finalised on 2016-11-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Zopiclone Orion, 3.75 mg, film-coated tablet is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The application for Zopiclone Orion, 7.5 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Imovane, 7.5 mg, film-coated tablet authorised in Denmark since 1986, with Sanofi-aventis Denmark A/S as marketing authorisation holder.

The reference product used in the bioequivalence study is Zimovane®, 7.5 mg, film-coated tablet from United Kingdom with Sanofi as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Zopiclone, 7.5 mg, tablet with Zimovane, 7.5 mg, film coated tablet under fasting conditions. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of zopiclone were determined with an adequately validated UPLC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

From a pharmacokinetic point of view, absence of studies with the additional strength, 3.75 mg is acceptable, as the pharmacokinetics of zopiclone is linear between 5 mg and 15 mg. It is found unlikely that there should be any marked non-linearity in pharmacokinetic between 3.75mg and 5 mg.

Based on the submitted bioequivalence study, Zopiclone Orion is considered bioequivalent with Zimovane.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The 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 Orion.

Safety specification
Summary table of safety concerns are listed below as in provided in the updated RMP version 1.2, dated 16-11-2016, by the applicant. The list is updated and is acceptable.

Important identified risks	Respiratory depression Anterograde amnesia Psychiatric and paradoxical reactions Tolerance and dependence Withdrawal symptoms/insomnia
Important potential risks	Abuse and diversion
Missing information	Use during pregnancy Use during lactation

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Zopiclone Jubilant, NL/H/2914/001/MR and Venlafaxin Orion, DE/H/1420/01-02/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Zopiclone Orion, 3.75 mg and 7.5 mg, film-coated tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Zopiclone Orion, 3.75 mg and 7.5 mg, film-coated tablet was positively finalised on 2016-11-30.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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