

Public Assessment Report

Scientific discussion

Zopiklon Evolan (zopiclone)

Asp no: 2024-0498, 2024-0499

This module reflects the scientific discussion for the approval of Zopiklon Evolan. The procedure was finalised on 2025-06-18. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Zopiklon Evolan, 5 mg and 7.5 mg, film-coated tablet.

The active substance is zopiclone. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Zopiklon Evolan, 5 mg and 7,5 mg, respectively, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Imovane, 5 mg, film-coated tablet, authorised in Sweden since year, with Viatrix AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Imovane, 7.5 mg, film-coated tablet, from Finland, with Sanofi Oy as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

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

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of zopiclone are well known. As zopiclone is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Zopiklon Evolan is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Zopiklon Evolan from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study with the 7.5 mg strength in the fasted state comparing Zopiklon Evolan with the reference product Imovane.

Pharmacokinetic properties of the active substance

Absorption: The bioavailability of zopiclone is about 80%. Peak plasma concentration is reached within 1-2 hours and is about 60 ng/ml after a dose of 7.5 mg. Absorption may be prolonged if zopiclone is not taken in an upright position.

The pharmacokinetics of zopiclone is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of zopiclone is linear within the dose range 5-15 mg.

Elimination: The half-life is 4-6 hours, increased to 7 hours in the elderly.

Study 17-VIN-0138

Methods

This was a single-dose, two-way crossover study conducted in 50 healthy volunteers, comparing Zopiclone, 7.5 mg, tablet with Imovane, 7.5 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of zopiclone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 26th January and 11th February 2018.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for zopiclone, n=44.

Treatment	AUC _{0-t} ng*h/ml	C _{max} ng/ml	t _{max} h
Test	559.7 $\pm$ 128.8	79.3 $\pm$ 16.9	0.67 (0.33 - 3.50)
Reference	542.6 $\pm$ 122.0	74.1 $\pm$ 19.5	1.00 (0.33 - 4.00)
*Ratio (90% CI)	103.04 100.66- 105.48%	108.05 101.97 - 114.51%	-
AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

*calculated based on ln-transformed data

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%.

A biowaiver was sought for the additional strength of 5 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 5 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of zopiclone is linear between 5 and 15 mg.

Based on the submitted bioequivalence study, Zopiklon Evolan is considered bioequivalent with Imovane.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Zopiklon Evolan.

Part II Safety specification

The MAH has submitted the version 0.2 RMP dated 2024-12-04 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III Pharmacovigilance Plan

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

Part V Risk minimisation measures

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

Part VI Summary of the RMP

The summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.2 signed 2024-12-04 is considered acceptable.

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

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 PL 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 generic product, Zopiklon Evolan, is found adequate. There are no objections to approval of Zopiklon Evolan, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Zopiklon Evolan, 5 mg and 7.5 mg, film-coated tablet was approved in the national procedure on 2025-06-18.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

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