LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zopiclone Grindeks
(zopiclone)

SE/H/2289/01-03/DC

This module reflects the scientific discussion for the approval of Zopiclone Grindeks. The procedure was finalised on 2024-08-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Zopiclone Grindeks, 3.75 mg, 5 mg, 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 Zopiclone Grindeks, 3.75 mg, 5 mg and 7.5 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following 25 concerned member states as CMS: AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SI and SK. Application was withdrawn in UK(NI) during validation period.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Imovane, 3.75 mg, film-coated tablet, authorised in FR since 2002, with Sanofi Aventis France as marketing authorisation holder.

The reference product used in the bioequivalence study is Imovane, 7.5 mg, film-coated tablet from HU with SANOFI-AVENTIS Zrt. as marketing authorisation holder.

European Reference Product (ERP)

Strength 01 (3.75 mg):

A European Reference Product is used in RMS and all CMS: Imovane, 3.75 mg, film-coated tablet, authorised in FR since 2002, with Sanofi Aventis France as marketing authorisation holder. The justification to use this product is based on information received from FR. The ERP information from FR was received and further circulated by RMS during the validation period.

Strength 02 (5 mg):

A European Reference Product is used in all CMS except for AT, FI and NO: Imovane, 5 mg, film-coated tablet, authorised in SE since 1991, with Viatris AB as the current marketing authorisation holder. The justification to use this product is based on RMS's own files. The ERP information was circulated by RMS during the validation period while the marketing authorisation holder was still Meda AB (within the same GMA). The MAH transfer from Meda AB to Viatris AB occurred during the validation period for this application (October 2022).

Another European Reference Product is used in CMS AT: Imovane, 5 mg, film-coated tablet, harmonised with acquis communitaire in FI since 2009, with SANOFI OY as marketing authorisation holder. The justification to use this product is based on information received from FI. The ERP information from FI was received by AT and RMS prior the start of procedure.

Strength 03 (7.5 mg):

A European Reference Product is used in CMS LT, BG, CZ, HR, NL, PT, SI and SK: Imovane, 7.5 mg, film-coated tablet, authorised in SE since 1991, with Viatris AB as the current marketing authorisation holder. The justification to use this product is based on RMS's own files. The ERP information was circulated by RMS during the validation period while the marketing authorisation holder was still Meda AB (within the same GMA). The MAH transfer from Meda AB to Viatris AB occurred during the validation period for this application (October 2022).

Another European Reference Product is used in CMS AT: Imovane, 7.5 mg, film-coated tablet,

authorised in FR since 1984, with Sanofi Aventis France as marketing authorisation holder. The justification to use this product is based on confirmation received from FR.

Potential similarity with orphan medicinal products
Not applicable

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, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Zopiclone Grindeks is a generic product, it will not lead to an increased exposure to the environment. Historical consumption data between 2017 and 2021 show a decreasing consumption trend. A Phase I+ (Phase I and, if needed, Phase IIA and IIB) environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Zopiclone Grindeks from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted one bioequivalence study comparing Zopiclone Grindeks with the reference product Imovane.

Pharmacokinetic properties of the active substance
Absorption: The bioavailability of zopiclone is approximately 80%. Maximal plasma concentration is reached within 1.5-2.0 hours and is approximately 30 ng/ml and 60 ng/ml after a dose of 3.75 mg and 7.5 mg respectively. The absorption is not affected by food and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics is linear within the range of 5-15 mg (Gaillot et al 1983).

Zopiclone is racemic, however the absorption half-lives and T_{max} values are not significantly different between the two enantiomers (Fernandez 1993). The S-enantiomer is approximately 50 times more potent than the R-enantiomer.

Elimination: The terminal half-life of zopiclone is 5 hours (7 hours in elderly).

Study ZOP-0322-29 – 7.5 mg, fasted
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Zopiclone, 7.5 mg, film-coated tablets with Imovane 7.5 mg film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 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 2022-06-16 and 2022-07-28.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for zopiclone, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**458.70 ±96.45**	**78.853 ±17.51**	**0.75 (0.50-3.50)**
Reference	**476.45 ±104.64**	**81.060 ±20.36**	**0.75 (0.50-4.00)**
***Ratio (90% CI)**	**96.45 (93.86-99.11)**	**98.05 (89.47-107.46)**	**-**
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 strengths of 3.75 mg and 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 strengths of 3.75 mg and 5 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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 mg – 15 mg and it is found unlikely that there should be any marked non-linearity in pharmacokinetic between 3.75 mg and 5 mg.

Based on the submitted bioequivalence study, Zopiclone Grindeks 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 Zopiclone Grindeks.

Part II Safety specification
The MAH has submitted the version 1.2 RMP dated 2024-06-27 and proposed the following summary 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 has been updated as a consequence of the updated summary safety concerns. The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1.2 signed 2024-06-27 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 Latvian.

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, Zopiclone Grindeks, is found adequate. There are no objections to approval of Zopiclone Grindeks, 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

The decentralised procedure for Zopiclone Grindeks, 3.75 mg, 5 mg, 7.5 mg, film-coated tablet was positively finalised on 2024-08-21.

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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)

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