Public Assessment Report

Scientific discussion

Zopiclone Jubilant 7.5 mg, film-coated tablets

(zopiclone)

NL/H/2914/001/MR

Date: 1 December 2014

This module reflects the scientific discussion for the approval of Zopiclone Jubilant 7.5 mg. The procedure was finalised at 4 October 2013. 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, the Member States have granted a marketing authorisation for Zopiclone Jubilant 7.5 mg, film-coated tablets from Jubilant Pharmaceuticals N.V.

The product is indicated for short-term treatment of insomnia.
Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Imovane 7.5 mg, tablets (NL License RVG 11063), which has been registered in the Netherlands since 14 April 1987 by Sanofi-Aventis Netherlands B.V.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Zopiclone Jubilant 7.5 mg is a white, round, biconvex film-coated tablet. The tablets are scored on one side and can be divided into equal doses

The product is packed in PVC/PVDC/Al blisters.

The excipients are:
Tablet core - calcium hydrogen phosphate dihydrate (E341), lactose monohydrate, maize starch, sodium starch glycolate, magnesium stearate (E470b)
Film-coating - hypromellose (E464), propylene glycol (E1520), titanium dioxide (E171), talc (E553B)

II.2 Drug Substance

The active substance is zopiclone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or slightly yellowish powder, which is slightly soluble in water. It is a racemic mixture of R and S isomers. The active substance exhibits polymorphism, and polymorphic form A is used.

The CEP procedure is used for both manufacturers the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the specification of the Ph.Eur. and CEP holder. As compendial analytical methods are used, submission of validation data is not required. Sufficient batch analysis results have been provided, demonstrating compliance with the specifications.

Stability of drug substance
For both manufacturers, the active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. For the bioequivalence study the reference product Immovane from the Belgian market has been used. The choice of the reference product is justified. Dissolution profiles of the innovator products from the member states involved, the proposed product and the biobatch have been compared. All batches show fast dissolution and have similar profiles.
The MAH has provided data on the breakability of the 7.5 mg tablets, demonstrating that the tablet halves comply with the demands in the Ph.Eur. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process starts with weighing, sieving and mixing of core ingredients, followed by drying, blending and tablet compression. Finally the tablets are coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches from one production site and two full-scale batches for a second site. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, dimensions, uniformity of dosage units, hardness, friability, loss on drying, dissolution, disintegration and microbiological purity. The release and shelf life specifications are completely identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on five full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) at the first production site. Stability data for the second manufacturer has been provided on three pilot-scale batches stored at 25°C/60% RH (12 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months) and two production scaled batches stored at 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Alu blisters. Stability results at accelerated storage conditions are out of specification. At intermediate and long-term storage conditions all results met the specification requirements. The product is not sensitive to light.
Based on the results provided, a shelf life of 36 months has been granted. The storage conditions granted are “do not store above 25°C”.
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Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is prepared from milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption (Complies EU food hygiene regulations). The production of calf rennet complies with the requirements defined in regulation 999/2001 and other applicable EU legislation.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Zopiclone Jubilant 7.5 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments regarding quality were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This generic application refers to information that is contained in the pharmacological-toxicological part of the dossier of the authorisation of the reference product. The MAH has not provided additional studies and further studies are not required.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since zopiclone is 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.3 Discussion on the non-clinical aspects

Reference is made tot the preclinical data obtained with the innovator product Imovane, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Zopiclone is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Zopiclone Jubilant 7.5 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Imovane® 7.5 mg tablets (Aventis Pharma SA-NV, Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects with mean age of 25.9 years. Each subject received a single dose (7.5 mg) of one of the 2 zopiclone formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 18 and 24 hours after administration of the products.

The study design is acceptable taking into account the pharmacokinetic profile of zopiclone with t_{max} of 1 – 1.5 hours and a half-life of 3.5 – 6.5 hours.

Zopiclone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substance. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Twenty-three subjects completed the treatment phase and were included in the pharmacokinetic evaluation. One subject was withdrawn during washout due to furuncle and intertrigo, another person was withdrawn at pre-admission for period II due to chicken pox, and a third subject was withdrawn on the day of the dosing on period II due to inflammation of a bee sting.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of zopiclone under fasted conditions.

Treatment N=23	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	420.8 ± 129.3	471.6± 145.1	93.4± 31.5	0.75 (0.50-2.67)	5.2 ± 1.8
Reference	434.6 ± 122.2	481.7± 137.1	84.9± 27	1.00 (0.50-3.50)	5.1 ± 1.8
***Ratio (90% CI)**	0.95 (0.89-1.01)	0.96 (0.91-1.01)	1.04 (0.91-1.20)	--	--
CV (%)	11.7	10.0	28.1	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Zopiclone Jubilant 7.5 mg is considered bioequivalent with Imovane® 7.5 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

Initially the MAH did not submit a risk management plan. After finalisation of the MRP, an RMP was provided, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Zopiclone Jubilant.

Routine risk management is considered sufficient for this medicinal product. The member states agree that no additional pharmacovigilance activities are deemed necessary.
The important identified risks, important potential risks and missing information are given below.

Summary table of safety concerns as approved in RMP

Important identified risks	– Respiratory depression – Anterograde amnesia – Psychiatric and paradoxical reactions – Impaired ability to drive and operate machinery and accidents – Tolerance and dependence – Withdrawal symptoms/ insomnia
Important potential risks	– Sleep walking and associated behaviour (e.g. sleep driving, sleep eating) – Abuse and diversion – Falls and fractures (mostly elderly) – Interaction with alcohol – Interaction with CNS depressing medicinal products – Interaction with moderate to severe CYP3A4 inhibitors or inducers – Use in pregnancy
Missing information	– Use during lactation – Children younger than 18 years

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Imovane. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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. After a pre-round with 2 participants, two cohorts of 10 participants were interviewed. The participants tested were between 18 and 70 years of age, with variable education level, male as well as female. Diagnostic testing was performed. Questions (17 in total) were asked about all parts of the leaflet. After the pre-round, as well as after the first round with 10 participants, no amendments of the PIL were considered necessary.
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

Zopiclone Jubilant 7.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Imovane 7.5 mg, tablets. Imovane is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors. Zopiclone Jubilant 7.5 mg, film-coated tablets was authorized in the Netherlands on 27 September 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential

similarity has been demonstrated for Zopiclone Jubilant with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 4 October 2013.

The following post-approval commitment has been made during the procedure:

- The MAH committed to submit a Risk Management Plan. This commitment has been fulfilled.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Introduction of the Risk Management Plan.	NL/H/2914/ 001/II/001	II	24-12-2013	6-9-2014	Approval	No