COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Zolpidemtartraat Aurobindo 5 mg and 10 mg, film-coated tablets

(zolpidem tartrate)

NL/H/4052/001-002/DC

Date: 7 August 2018

This module reflects the scientific discussion for the approval of Zolpidemtartraat Aurobindo 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 19 April 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zolpidemtartraat Aurobindo 5 mg and 10 mg, film-coated tablets, from Aurobindo Pharma B.V.

The product is indicated for short-term treatment of insomnia in adults. Benzodiazepines or benzodiazepine-like agents 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 decentralised procedure concerns a hybrid and generic application for claiming essential similarity with the innovator product Stilnoct 10 mg, tablets which has been registered in the Netherlands by Sanofi-aventis Netherlands B.V since 15 June 1989.

The concerned member states (CMS) involved in this procedure were:
Zolpidemtartraat Aurobindo 5 mg - Luxembourg
Zolpidemtartraat Aurobindo 10 mg - Czech Republic, Germany, Spain and Poland.

The marketing authorisation for the 10 mg strength has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic medicinal product). For the 5 mg strength the legal base is Article 10(3) of Directive 2001/83/EC (hybrid medicinal product), as there is no European reference product authorised for the strength of 5 mg that the MAH can refer to as a generic application.

II. QUALITY ASPECTS

II.1 Introduction

Zolpidemtartraat Aurobindo 5 mg is a white to off-white, circular, biconvex film-coated tablet, debossed with “E” on one side and “78” on the other side.

Zolpidemtartraat Aurobindo 10 mg is white to off-white, oval shaped, biconvex film-coated tablet, debossed with “E” on one side and “80” with a score line between “8” and “0” on the other side. The tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PVdC Aluminium foil blisters and HDPE bottles packs with polypropylene screw cap closure.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (PH-101), sodium starch glycolate (Type A) and magnesium stearate

Film-coating – hypromellose, macrogol 400, titanium dioxide (E171)

II.2 Drug Substance

The active substance is zolpidem tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, hygroscopic, crystalline powder. Zolpidem tartrate is slightly soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride. The active substance shows polymorphism. Polymorphic form A is adequately substantiated.

The CEP procedure is used for 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for an appropriate amount of batches.

Stability of drug substance
The active substance is stable for 36 months 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. A bioequivalence study has been performed with the 10 mg film-coated tablets. In addition, dissolution studies have been performed between the test product and reference product and between the 10 mg film-coated tablets and 5 mg film-coated tablets is order to establish the similarity. The results show that the dissolution studies in both situations can be considered as similar. A test for subdivision of the 10 mg film-coated tablet was performed in accordance with the Ph.Eur. The data show that the tablet can be divided into two equal halves. Overall, the pharmaceutical development of the study has been adequately performed.

Manufacturing process

The manufacturing process involves sifting, mixing, granulating, drying, milling, lubrication, compression, preparation of the coating solution, coating and packing. This process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All specifications comply with the corresponding Ph. Eur. monograph. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units, subdivision of tablets, related substances, assay, thickness, microbial contamination, specified micro-organisms, identification of titanium dioxide and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from a sufficient amount of batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two batches of each strength stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. A photostability study showed that the product is not sensitive to light. Based on the provided stability data, the proposed self-life of 36 months with no special storage conditions for the drug product is considered acceptable.

Subdivision of tablets of the 10 mg product was checked at regular intervals during the long-term stability study, including the final time point (48 months). The results show that subdivision remains stable during the shelf-life of the 10 mg product. The batches comply with the requirements at all time-points measured. Hence, the MAH has adequately shown that the tablets can be broken in two equal halves during the full shelf-life of the product.

Stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The excipient lactose monohydrate is derived from the milk of healthy animals in the same conditions as milk for human consumption and is prepared with the use of calf rennet. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal

Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zolpidemtartraat Aurobindo is intended for generic and hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic/hybrid formulation of Stilnoct which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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

Zolpidem tartrate 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 and hybrid 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 Zolpidemtartraat Aurobindo 10 mg, film-coated tablets (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Stilnoct 10 mg, tablets (Sanofi-aventis Netherlands B.V, NL).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

According to the bioequivalence guideline, the following general requirements must be met where a waiver for additional strength(s) is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content
ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed
iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths
iv. appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

In addition, the drug product should have linear pharmacokinetics in the therapeutic dose-range.

The MAH presented the composition of the test products and dissolution data as support for the biowaiver for the additional strength 5 mg. Both 5 and 10 mg strengths of the test product have the same qualitative composition and are quantitatively dose-proportional. The comparative dissolution data between the test biobatch 10 mg and the additional strength 5 mg demonstrated similarity at pH 1.2, 4.5 and 6.8 as both dissolved very rapidly, with more than 85% of the drugs dissolved within 15 minutes (see also Quality AR). Bioequivalence appears to be demonstrated using the 10 mg strength. Overall, all the criteria for a biowaiver based on the current Guideline on the Investigation of Bioequivalence are met.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 20-45 years. Each subject received a single dose (10 mg) of one of the 2 zolpidem tartrate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00 and 16.00 after administration of the products.

The design of the study is acceptable. A single dose study under fasting conditions using the high strength is considered sufficient to support an application for the proposed immediate-release products. The proposed products can be taken with and without food. Hence, a study in the fasting condition is agreed as this more sensitive to detect differences between the test and reference product in accordance to the Guideline on the Investigation of Bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is 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

Seven subjects were withdrawn from the study. Three subjects were withdrawn due to vomiting and four subjects were eligible for pharmacokinetic analysis. Therefore, a total of 41 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	854.9 ± 435	911.0 ± 410	192.0 ± 65	0.83 (0.33 – 2.5)
Reference	817.6 ± 359	860.6 ± 404	192.5 ± 59	0.67 (0.17 – 4.0)
***Ratio (90% CI)**	0.10 (0.93 – 1.07)	--	0.99 (0.92 – 1.07)	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Zolpidemtartraat Aurobindo is considered bioequivalent with Stilnoct.

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).

The results of study 427-14 with 10 mg formulation can be extrapolated to other strengths 5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Zolpidemtartraat Aurobindo.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Dependence and withdrawal symptoms/rebound effect - Psychiatric and paradoxical reactions - Additive CNS depressant effects when administered with alcohol or CNS depressant - Coma/respiratory depression during overdose - Drug abuse
Important potential risks	- Suicidality in patients with depression, severe depression or suicidal ideation
Missing information	- Use in children and adolescents under 18 years of age - Use during pregnancy - Use during nursing/breastfeeding

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Stilnoct. 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/hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zolpidem Aurobindo 5 mg & 10 mg film-coated tablets. The proposed PL there was accepted in September 2013 during mutual recognition procedure PT/H/0866/001-002/MR. The key messages for safe use, design and the layout of the PL for Zolpidemtartraat Aurobindo is similar to that of Aurobindo. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zolpidemtartraat Aurobindo 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic and hybrid forms of Stilnoct 10 mg, tablets. Stilnoct 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.

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 Zolpidemtartraat Aurobindo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 April 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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