CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zolpidemtartraat 5 mg and 10 mg PCH, film-coated tablets Pharmachemie B.V., the Netherlands

zolpidem tartrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1585/001-002/DC
Registration number in the Netherlands: RVG 103724, 103728

6 May 2010

Pharmacotherapeutic group:	hypnotics and sedatives, benzodiazepine related drugs
ATC code:	N05CF02
Route of administration:	oral
Therapeutic indication:	short term treatment of insomnia
Prescription status:	prescription only
Date of authorisation in NL:	6 April 2010
Concerned Member States:	Decentralised procedure with AT, CZ, EE, EL, ES, IE, LT, LV, NO, PT, SE, SI, SK; 10 mg only – IT, RO
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Zolpidemtartraat 5 mg and 10 mg PCH, film-coated tablets from Pharmachemie B.V. The date of authorisation was on 6 April 2010 in the Netherlands. The product is indicated for Short term treatment of insomnia.

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 SPC.

Zolpidem, an imidazopyridine is a benzodiazepine-like hypnotic agent. In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant or anxiolytic effects. These effects are related to a specific agonist action at central receptors belonging to the ”GABA-omega” (BZ1 & BZ2) macromolecular receptor” complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Stilnox 10 mg which has been registered in France by Sanofi-aventis France since 1987. In the Netherlands, Stilnoct 10 mg (NL license RVG 13223) has been registered since 1989. In addition, reference is made to Stilnox authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC for the 10 mg strength, and on article 10(3) of Directive 2001/83/EC, hybrid application, for the 5 mg strength. Reference is made to the 10 mg strength.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Stilnox 10 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic medicinal product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is zolpidem hemitartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white to almost white, crystalline powder. The active substance is sparingly soluble in water and methanol and practically insoluble in methylene chloride. Zolpidem hemitartrate does not exhibit isomerism or polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of 4 main steps. No class 1 organic solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in line with the Ph.Eur., with additional requirements for heavy metals, residual solvents, related substances, assay by HPLC, microbial contamination and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches from one manufacturer and 3 pilot-scale batches from the other supplier.

Stability of drug substance
Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) and 5 pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes were seen under both conditions. The proposed retest period of 24 months for the drug substance could be granted, when packed into the original packaging in order to protect from light.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Zolpidemtartraat 5 mg PCH is a white, oval, biconvex, film-coated tablet, embossed with "ZIM" on one side and "5" on the other side.
Zolpidemtartraat 10 mg PCH is a white, oval, biconvex, film-coated tablet, scored on both sides and embossed with "ZIM 10" on one side.
The tablet can be divided into equal halves.

The different tablet strengths are dose proportional.

The film-coated tablets are packed in PVC/PE/PVDC-Al blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate Type A, hypromellose (E464), magnesium stearate (E572).
Coating - hypromellose, titanium dioxide (E171), macrogol 400.

The different strengths of drug product are manufactured dose proportionally.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies that have been performed were in respect to characterizing the originator product. The choice of the packaging material and manufacturing process are justified. The composition of the batches used in the bioequivalence studies is the same as the final product composition.
The dissolution profiles were compared of the biobatch, a 5 mg, a 10 mg tablet and a halved 10 mg tablet and all European innovator products. All dissolution profiles are essentially similar. The 10 mg tablets can be broken by hand and these halves were used in the uniformity of mass test for the halved tablets. The halve tablets of the 10 mg tablets can be considered equal to the 5 mg tablets as also the dissolution profile is essential similar. Although compliance with the current Ph.Eur. criteria for breaking tablets was not demonstrated during validation, the correct specification is included in the specifications and compliance was shown during batch analyses.
Comparative dissolution studies have been performed between the 10 mg test bio-batch and the 10 mg DE reference product. The dissolution results of both products are > 85% after 15 min. Stilnoct 10 mg from the DE and NL market show identical dissolution profiles.
The pharmaceutical development has been adequately described.

Manufacturing process
The manufacturing process consists mainly of the preparation of the pre-compression blend, compression this blend into tablets and film-coating of these tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented at least three production batches per strength.

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

Quality control of drug product
The product specification includes tests for appearance, identity, uniformity of mass / average mass, uniformity of broken tablets (10 mg), hardness, disintegration time, water content, dissolution, content uniformity, assay, impurities and microbial quality. The release and shelf-life requirements are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on at least three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches and seven pilot-scale batches of 5 mg tablets and on four full-scale and seven pilot-scale batches of 10 mg tablets stored at 25°C/60% RH (48 to 60 months) and 40°C/75% RH (6 to 12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVDC/Al-blisters. No changes were seen under both conditions. Photostability studies show a slight decrease in assay, indicating that the drug product is sensitive to light. The proposed shelf life of 36 months could be granted, if stored in its original package in order to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Besides lactose, no excipients of animal origin are used in the formulation. The lactose used is obtained from cow's milk as for human consumption. A BSE statement and a statement that no risk exists for dioxin contamination have been provided.

II.2 Non clinical aspects

This product is a generic formulation of Stilnox, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of zolpidem tartrate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Zolpidem tartrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Zolpidemtartraat 10 mg PCH (Pharmachemie B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Stilnox 10 mg tablets (Sanofi-aventis, Germany).

The choice of the reference product
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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 18-38 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 a fasting period of 10 hours. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at t 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 15, and 24 hours after administration of the products.

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.
Two member states considered that the long term stability for the samples in the bioequivalence study has not been sufficiently evaluated, and therefore considered the analytical results uncertain. In response to this, the MAH committed to provide appropriate stability data of zolpidem in blood plasma.

Results
There was one withdrawal. The remaining 41 subjects completed the study and were eligible for pharmacokinetic analysis.

Drug related adverse events were: blurred vision (4 Reference product, 7 Test product); hiccup (1 Reference product, 1 Test product); double vision (1 Reference product, 1 Test product) and headache (3 Reference product, 1 reference product).

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	**$t_{1/2}$** h
Test	494 ± 246	505 ± 249	171 ± 61	0.75 (0.25-1.75)	-
Reference	488 ± 258	500 ± 262	163 ± 48	0.75 (0.50-1.50)	-
***Ratio (90% CI)**	1.00 (0.92-1.10)	1.01 (0.92-1.10)	1.02 (0.96-1.09)	-	-
CV (%)	24	23	17	-	-

$AUC_{0-\infty}$ 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 in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of zolpidem tartrate under fasted conditions, it can be concluded that Zolpidemtartraat 10 mg PCH and the Stilnox 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Zolpidem tartrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of zolpidem tartrate. 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.

Extrapolation to 5 mg tablet
The 10 mg tablets are dose proportional with the 5 mg tablets. A biowaiver to the 5 mg strength is acceptable as all criteria according Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 are met.

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).

Risk management plan
Zolpidem tartrate was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of zolpidem tartrate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC is in accordance with the SPCs for the MRP procedures NL/H/251/01-02, NL/H/256/01-02, NL/H/259/01-02 and NL/H/260/01-02, concerning other zolpidem tartrate generics.

Readability test
The package leaflet has been harmonised with the PL of the Procedures NL/H/0251-0261/001-002/MR and NL/H/0266-0268/001-002/MR. Bridging of the current PIL to the one of these procedures is acceptable because the medicines are in the same therapeutic class and the key safety information set out in the SPC is similar. An acceptable bridging report has been provided.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zolpidemtartraat 5 mg and 10 mg PCH, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Stilnox film-coated tablets. Stilnox 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other zolpidem tartrate containing products.

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 5 mg and 10 mg PCH, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 27 October 2009. Zolpidemtartraat 5 mg and 10 mg PCH were authorised in the Netherlands on 6 April 2010.

A European harmonised birth date has been allocated (9 June 1987) and subsequently the first data lock point for zolpidem tartrate is June 2010. The first PSUR will cover the period from October 2009 to June 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 March 2014.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to provide appropriate stability data of zolpidem in blood plasma.
- The MAH committed not to market the product in CZ until sufficient long-term stability of zolpidem in blood plasma has been provided.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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