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/1315/001/MR
Registration number in the Netherlands: RVG 33042

6 April 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 first authorisation in NL: 12 October 2005
Concerned Member States: Mutual recognition procedure with BE and LU
Application type/legal basis: Directive 2001/83/EC, Article 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 Zolpidem Eurogenerics bru 10 mg effervescent tablets, from Eurogenerics N.V. The date of authorisation was on 12 October 2005 in the Netherlands. The product is indicated for the short term treatment of insomnia.

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

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application.

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.

Since marketed zolpidem reference products are film-coated tablets, containing 5 or 10 mg zolpidem tartrate, and the product under consideration is a 10 mg effervescent tablet, it may not be possible to establish essential similarity, as differences in rate of absorption are anticipated. Directive 2001/83/EC, Article 10(3) enables the possibility of using references to an originator dossier (without the originator’s consent) in order to support a generic application not just for essentially similar products, but also in other cases such as covering more or other indications, strengths and pharmaceutical forms than the originator products, if sufficient bridging data are submitted by the applicant. Therefore, the current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 “Clinical Aspects”.

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

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, since this is not required for generics.
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 this product type 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.*). The active substance is a white or almost white hygroscopic, crystalline powder, which is sparingly soluble in water and methanol and practically insoluble in methylene chloride. Zolpidem hemitartrate does not exhibit isomerism or polymorphism.

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 new 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the Ph.Eur. monograph, CEP, and an additional limit for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three production-scale batches. The specification for the particle size has been adequately established during pharmaceutical development of the finished product.

Stability
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (36 months) and at 40°C/75%RH (36 months). The stress testing results show that a rapid degradation can be observed for the samples boiled with two specific HCl concentrations, and when the sample is treated with high temperature.

During the long term and accelerated stability studies the appearance, clarity and colour of the solution remain unchanged upon storage. The content of water increases for all batches under both storage conditions in both types of packaging material. It can be concluded from the results and found in the Ph.Eur. monograph that zolpidem tartrate is hygroscopic and is able to store water. Therefore, the uptake of water during storage is to be understood as a common, non-adverse process which ends at a determined level. Moreover, the related substances remain unchanged upon storage, while the assay shows some limited degradation.

Based on the data submitted, a retest period could be granted of 36 months without specific storage conditions.
The MAH has committed to put 1 batch on stability yearly, and to put 3 validation batches on stability. In case of any change in the manufacturing the first three batches will be put on stability.

* 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
Zolpidem Eurogenerics bruïs, effervescent tablets contain as active substance 10 mg of zolpidem tartrate, and are oblong-formed, biplane, with bevel-edges and score-lines on both sides. The tablet can be divided into equal halves.

The effervescent tablets are packed in Al/Al blisters in a carton box with a HDPE tablet container with LDPP screw cap containing desiccant, or in a carton box containing a OPA/Alu/PVC//Alu blister.

The excipients are: disodium citrate E331, monosodium citrate E331, sodium hydrogen carbonate E500, saccharin sodium E954, lactose monohydrate, povidone E1201, macrogol, anhydrous sodium carbonate E500, magnesium stearate E470B, grapefruit flavour.

Pharmaceutical development
The purpose of formulation development was the development of an effervescent tablet with a maximum weight of 300 mg which disintegrates rapidly in approximately 50 ml of water in a well-tasting active ingredient solution, adequately masking the bitter taste of the active ingredient. The packaging and excipients are usual for effervescent tablets. Zolpidem tartrate is hygroscopic. Choices for lubricant, internal desiccant and flavour have been justified. A grapefruit taste is added to mask the bitter taste of the active substance.

The MAH produced five types of effervescent bodies of varying composition and determined the disintegration time of these tablets. It turned out that the tablets with disodium citrate, monosodium citrate and sodium hydrogen carbonate resulted in the best effervescent tablets regarding reproducibility and stability. The development of the effervescent tablet is satisfactorily explained.

Excipients
The excipients comply with the Ph.Eur. requirements, except for disodium citrate E331, which complies with the monograph in the British pharmacopoeia (BP), and monosodium citrate E331 which is conform in-house specifications. This in-house monograph is based on the Ph.Eur. monograph and the BP monograph for disodium citrate. These specifications are acceptable.

Manufacturing process
The tablets are manufactured by granulation of the active substance and effervescent components with povidone and ethanol. After addition of the other excipients and a blending step, the tablets are pressed and packed. Suitable in-process controls have been set. Validation data have been provided for pilot-scale batches. Full-scale validation data will be provided of the first production batches.

Container closure system
The MAH has submitted in-house specifications for all types of packaging materials which include among others identification and dimensions. For the drying agent a specification for loss on drying has also been included. For all plastic materials an IR-spectrum was submitted and a declaration that it complies with Directive 90/128/EEC. For the plastic tubes a declaration for the compliance with the Ph.Eur. was submitted. Finally for the drying agent a declaration on compliance with Directive 94/62/EG was provided. For all packaging materials analysis results showing compliance with the specifications were submitted.

Quality control of drug substance
The product specification includes tests for appearance, colour, dimensions, friability, resistance to crushing, disintegration in 50 ml of water, pH of solution, uniformity of mass of whole and halved tablets, loss on drying, identity and assay active substance, by-products and degradation products and microbial quality. The release requirements are acceptable. Methods have been described and validated sufficiently. Results of batch analysis have been provided for pilot-scale batches. Results of full-scale batches will be provided when available.
Stability tests on the finished product

Stability data on the product have been provided for three pilot-scale batches (in both types of packaging materials) in accordance with applicable European guidelines. In case of long-term exposure to light, the active ingredient discolours to yellow. Based on the data submitted, a shelf life was granted of 3 years with storage condition: ‘Store in the original packaging in order to protect from moisture’.

Stability of the divided tablets (removed from aluminium blisters)

If removed from aluminium blisters the residual half tablet must be stored anyway until the next application. The MAH has performed a separate stability study demonstrating the suitability of divided tablets after open storage for a few days. Some tablets (stored in aluminium blisters) had been divided into halves. These parts were stored at 25°C/65% RH and after 1, 2, 3 and 6 days the critical characteristics were tested.

The pharmaceutical quality of the dosage form "effervescent tablet" was checked by "loss on drying" and "disintegration". The chemical stability of the active ingredient was proven by assay and determination of impurities. Additionally, the equilibrium relative humidity was recorded, which is an important criterion for preparations or substances sensitive to humidity.

On request of the RMS a remark on storage of halved tablets has been included in section 6.4 of the SPC: ‘Non-administered half tablets must be wrapped in the aluminium blister together with the other tablets in the carton box and stored in a dry place. A tablet half stored in such a way, must be used within 24 hours.’

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

The magnesium stearate used is of vegetable origin. For lactose monohydrate a declaration of the supplier has been submitted that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption. The calf rennet used for production of raw material whey is in accordance with Public Statement EMEA/CPMP/571/01 rev. 1 of February 2002. The sourcing of the milk is constantly, officially supervised according to the milk hygiene Directive 92/46/EEC. Grapefruit flavour is not derived from specified risk material.

II.2 Non clinical aspects

This active substance has been available on the European market for 20 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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

Bioequivalence/ Waiver
In order to obtain a biowaiver, an extensive expert report was submitted to support this application. Reference is made to ‘Relating issues’ in the ‘Note for Guidance on the investigation of bioavailability and bioequivalence’.

See below the arguments of the MAH for a biowaiver for Zolpidem Eurogenerics bruïs, effervescent tablets:

A) Characteristics related to the active substance
a.i. Risk of therapeutic failure or adverse drug reactions
Reference is made to literature indicating that zolpidem has a wide therapeutic window and a low risk for adverse drug reactions, in the expected range of plasma levels.

a. ii. Risk of bio-in-equivalence
The MAH stated that there is no evidence that any bioavailability problems exist with zolpidem tartrate that may lead to bio-in-equivalence. The pharmacokinetics of zolpidem tartrate is linear over the dose range of 5 - 20 mg. In general practise only doses of 5 and 10 mg are given. At the time of application, only normal release tablets were marketed. The normal release tablet is taken with water while the effervescent tablet has to be taken after dissolution of this tablet.

Differences in dissolution are also reflected in the dissolution profile, i.e. within 3 min for the effervescent tablet and within 10 min for the normal release tablet. After administration of the solution obtained by the effervescent tablet, comparable AUC values are expected with regard to reference Stilnox, as permeability, absorption and solubility are considered not problematic. With regard to the C<sub>max</sub>, it is not unlikely that this value will be higher after administration of the effervescent tablet compared with Stilnox, as the Stilnox tablet has to be dissolved before absorption. However, dissolving of the Stilnox tablet (the innovator) is known to be fast. This is also reflected in the observed t<sub>max</sub> values of 1.0 hours for zolpidem, according to the literature. Thus although absorption of zolpidem after administration of the solution can be more rapid from the gastro-intestinal tract compared to the Stilnox tablet, it is expected that this is moderately reflected in the C<sub>max</sub> values. This is further substantiated by submitted data from literature, where after comparable dose-normalised C<sub>max</sub> values were observed after either intravenous administration (5 mg) or oral administration (20 mg) of zolpidem. In addition, a slightly higher C<sub>max</sub> value after administration of the solution compared to Stilnox is acceptable and is not expected to lead to a higher incidence in adverse events. It is unlikely that a slightly different C<sub>max</sub> would affect efficacy.

a.iii. Solubility
The solubility of zolpidem tartrate can be considered to be high. The minimal required solubility (= 10 mg in 250 ml) was achieved. In addition, dissolution in the gastro-intestinal tract will not be a problem for the product to be registered, as it is taken as a solution (effervescent tablet).

a.iv. Pharmacokinetic properties
Zolpidem tartrate is rapidly absorbed in man (ca. 1 h). Zolpidem tartrate displays linear pharmacokinetics over the dose range of 5 - 20 mg. According to the literature, it can be estimated that at least 93% of the dose is absorbed (recovery primarily as metabolites in urine is ca. 56% and faeces is ca. 37%, see SPC). These data indicate that absorption is not problematic for zolpidem, and that its permeability can be considered high (also indicative is the log P of 2.44).

B) Characteristics related to the medicinal product
b.i. Rapid dissolution
The MAH compared the dissolution of the 10 mg Zolpidem tartrate Eurogenerics bruïs 10 mg effervescent tablets with that of reference product Stilnox 10 mg film-coated tablets (n=6). These dissolution profiles show that bioequivalence between both products is highly likely.
b.2. Excipients
The excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. The excipients are considered not to effect absorption or pharmacokinetics of zolpidem.

b.3. Manufacture
There is no indication that polymorphism and isomerism could be critical issues for zolpidem.

Conclusion bioequivalence / biowaiver
As zolpidem is considered highly permeable and well absorbable, and dissolution and solubility are considered non-problematic, in case of a solution of zolpidem, a waiver can be granted. The risk of bio-in-equivalence regarding the $C_{\text{max}}$ compared with Stilnox is not unlikely, but is considered not to result in a significantly altered safety or efficacy profile.

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

Readability test
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. Two rounds of diagnostic testing and scoring were performed in face-to-face interviews with 10 volunteers per round. The volunteers were selected according to age, gender and educational level. Fifteen questions were posed evaluating findability, understandability and applicability on key issues in the PL, as well as 16 open questions on lay-out and difficult wording of the PL. The ease of finding was also noted. Suggestions for improvement of readability of the PL were recorded.

Scoring criteria were set at 80% of volunteers to be able to find information and 80% to understand the leaflet text according to the readability guideline criteria (16 out of 20 volunteers).

After the first round of 10 volunteers, the scoring results were inadequate in two questions on finding the contra-indications and the indications. A short discussion on the cause of the misfindings was outlined. According to the MAH, due to obligatory wording of the contra-indication section, which is not everyday language, it was not found by 30% of the 20 volunteers as would be the case in other tests too. Once found, however, the understanding of the section was good. The question on the indications was not clear and thus the question was changed. This was acknowledged by the RMS.

Changes were made to the PL, taking into account the answers to the open questions. One of these changes was the addition of a sentence on combined use with alcohol. Thereafter another test-round was held with 10 volunteers. The results confirmed the results of test round 1 and over 90% was able to find and understand the leaflet.

The RMS remarks that scoring of changed text or questions cannot be taken as one outcome, in principle, in the overall scoring. Since overall all test results are positive, the total outcome of the readability test is acceptable.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zolpidem Eurogenerics bruis 10 mg effervescent tablets have a proven chemical-pharmaceutical quality and are a hybrid form of Stillnoct 10 mg tablets. Stillnoct is a well-known medicinal product with an established favourable efficacy and safety profile.

No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver. This has been sufficiently demonstrated.

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. Zolpidem Eurogenerics bruis 10 mg effervescent tablets was authorised in the Netherlands on 12 October 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that Zolpidem Eurogenerics bruis 10 mg effervescent tablets has been demonstrated to be an acceptable hybrid form of the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 12 August 2008.

The first PSUR will cover the period from August 2008 to August 2011, after which the second PSUR coincides with the first renewal in August 2013. Subsequently the PSUR submission cycle is 3 years.

The date for the first renewal will be: 12 August 2013.

The following post-approval commitment was made during the procedure:

Quality – active substance
- The MAH has committed to put 1 batch on stability yearly, and to put 3 validation batches on stability. In case of any change in the manufacturing the first three batches will be put on stability.

Quality - medicinal product
- The MAH committed to perform a photostability study in the PP/PE tablet container before the product will be marketed in Belgium.
- The MAH has committed to provide full-scale validation data of the first production batches.
- The MAH has committed to provide full-scale batches provided when available (quality control).
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\textsubscript{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\frac{1}{2} Half-life
\text{t}_{\text{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

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<th>Scope</th>
<th>Procedure number</th>
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