CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

DRETACEN 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets
Sandoz B.V, the Netherlands

levetiracetam (as hydrochloride)

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/2155/001-004/DC
Registration number in the Netherlands: RVG 108561, 108563-108565

25 January 2012

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX14
Route of administration:	oral
Therapeutic indication:	as monotherapy partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy; as adjunctive therapy in partial onset seizures with or without secondary generalisation in patients > 1 month of age with epilepsy; as adjunctive therapy in myoclonic seizures in patients > 12 years with Juvenile Myoclonic Epilepsy; as adjunctive therapy in primary generalised tonic-clonic seizures in patients > 12 years with Idiopathic Generalised Epilepsy.
Prescription status:	prescription only
Date of authorisation in NL:	21 September 2011
Concerned Member States:	Decentralised procedure with LT, PL and RO (all strengths), and BG, CZ (all strengths except 750 mg)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 DRETACEN 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets from Sandoz B.V. The date of authorisation was on 21 September 2011 in the Netherlands.

The product is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

The product is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

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

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.
The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra 250, 500, 750 and 1000 mg film-coated tablets which have been registered in the EEA by UCB Pharma through centralised procedure EU/1/00/146/001-029 since 29 September 2000 (original product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Keppra 1000 mg tablets, registered in the EEA and obtained from the Belgian market. 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. This generic product can be used instead of its reference product.

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 application.

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 levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Levetiracetam is a white to an off-white crystalline powder. The drug substance is soluble in water, in methanol, in chloroform and in alcohol. Levetiracetam is slightly hygroscopic. Levetiracetam exhibits isomerism, it contains one chiral center. Levetiracetam from the drug substance manufacturer is the S-enantiomer. Levetiracetam exhibits polymorphism; it has three crystalline polymorphic forms, known as Form-I, Form-II and Form-III. The drug substance manufacturer produces crystalline Form-I.

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/EMA 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 drug substance is manufactured by two manufacturers. The manufacturing process of one manufacturer consists of four steps, which include synthesis, drying, pulverising, sifting and packing. The other synthesizes the drug substance in a five-step process, which include mixing, crystallisation, isolation and purification. The information on the manufacturing process is deemed acceptable.

Quality control of drug substance
The MAH used the analytical methods described in the Ph.Eur. monograph with exception of the in-house methods for related substances. This method is cross-validated with the Ph.Eur. methods.
The MAH has partly adopted the specifications of levetiracetam presented in the DMFs of the suppliers with additional requirements for particle size distribution.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from both drug substance manufacturers.

Stability of drug substance
For one manufacturer, stability data on the active substance have been provided for 8 full-scale batches stored at 25°C/60% RH (5-60 months) and 4 batches stored at 40°C/75% RH (5-6 months). No changes or trends were seen at both storage conditions. Stability testing was completed with results at long-term conditions for up to 60 months for one single batch and up to 36 months for three batches.
For the oldest batches, no accelerated data has been provided. Based on the availability of 6 months accelerated and 36 months long-term stability data of the newly added batches, the claimed re-test period of 48 months can be granted.
For the other active substance supplier, stability data on the active substance have been provided for 3 batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) and for three batches stored at 30°C/65% RH (24 months) and 40°C/75% RH (6 months). Stability testing was completed with results at accelerated conditions for 6 months and long-term conditions for up to 5 years for 3 batches, tested at "old" specifications. For the three new batches; 6 month accelerated and 24 months long-term data are available. The stability results show that no significant changes or trends were observed at either long-term or accelerated storage conditions. In view of the provided stability data, the proposed re-test period of 5 years is justified.

In principle, the drug substance does not require specific storage conditions. However, the general label followed by one supplier already contains the information as "Protect from moisture, freezing, excessive heat and light. Do not expose to direct sunlight". Although protection from sunlight or high temperatures is not considered to be necessary, the storage condition can be accepted.

The MAH claimed his own re-test period of 1 year with the storage conditions: “Store in a well closed container protected from light, at temperature below 25 °C.”

** 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
DRETACEN is formulated as a film-coated tablet containing 250 mg, 500 mg, 750 mg or 1000 mg Levetiracetam. The drug products are described as light blue (250 mg), yellow (500 mg), apricot (750 mg) or white (1000 mg) coloured, oval shaped, biconvex film-coated tablets, scored on both sides and debossed with LVT/ 250, LVT/ 500, LVT/ 750 or LVT/ 1000 on one side.
The tablets can be divided into equal halves.

The tablets are packed in OPA/Al/PVC-Al blisters or HDPE bottles with PP closures containing a silica gel desiccant capsule.

The excipients are:
Core - povidone K25, microcrystalline cellulose, croscarmellose sodium, crospovidone (type A), colloidal anhydrous silica, talc, magnesium stearate
Coating - hypromellose, hydroxypropylcellulose, macrogol (PEG 6000), titanium dioxide (E171), talc, indigo carmine (E132) (250 mg), iron oxide yellow (E 172) (500 and 750 mg), iron oxide red (E 172) (750 mg)

The composition of the different strengths is dose proportional and the coating materials differ only in colouring agents.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The majority of the development was performed on the 1000 mg strength. The lower strengths are weight proportional to the highest strength.
Wet granulation was used as technological procedure of the tablet core preparation. Optimization of tablet composition and process parameters on laboratory scale was done on the 1000 mg strength. Levetiracetam is very soluble in water and has a pH independent solubility. To further evaluate the effect of pH on dissolution, tests were conducted at three pH values. More then 85% of levetiracetam is dissolved in 15 minutes in all different dissolution media. Three batches for each strength were tested. All dissolution profiles are similar to the dissolution profile of the bio-batch. Therefore, batch-to-batch uniformity is conformed. The MAH demonstrated that the dissolution profiles of the test and reference product are similar. From a chemical-pharmaceutical point of view the test and reference product are essentially similar. The pharmaceutical development of the product has been adequately performed.
The MAH demonstrated using the Ph.Eur. test for uniformity of mass of subdivided parts that the tablets of all strengths can be divided into equal halves.

Manufacturing process
The manufacturing process includes the following steps: granulation, blending with excipients and final blending with magnesium stearate, compressing the mixture and film-coating of the tablet cores
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-sized batches per strength.

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, water content, uniformity of dosage units by mass variation, identification of levetiracetam, identification of colorants, assay, residual solvents, dissolution, related substances and microbial quality.
The release and shelf life limits for water content are not identical all other parameters have the same release and shelf life limits.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full scaled batches per strength stored in an Al-Al blister or HDPE container at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The drug product is demonstrated to be photostable.
No changes in any of the parameters were observed. The proposed shelf life of 24 months and storage condition “Store in the original packaging in order to protect from light” are justified based on the data included.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

Good Laboratory Practice
This product is a generic formulation of Keppra, 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 levetiracetam 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

Levetiracetam 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 DRETACEN 1000 mg (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Keppra 1000 mg tablets (UCB Pharma, BE).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results with the EU reference product.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in healthy male (12) and female (14) subjects (aged 22 – 52 years, BMI 20-28 kg/m^2). Each subject received a single dose (1000 mg) of one of the 2 levetiracetam formulations. The products were 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 7 days.
Blood samples were collected at 0.17, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 4, 6, 10, 16, 24, 36 and 48 hours after administration of the products.

Analytical/statistical methods
The analytical method is adequately validated and 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
During the study, 5 subjects were withdrawn. Two subjects withdrew due to personal reasons, one was dismissed due to showing up late for period 2 check-in, one did not show up for period 2 check-in and one subject was dismissed due to a positive cotinine test on period 2 check-in.

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

Treatment N=21	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	292 ± 51	296 ± 53	31.8 ± 6.67	0.75 (0.5 – 4.0)	7.6 ± 1.1
Reference	292 ± 52	297 ± 54	32.6 ± 10.2	0.75 (0.33 – 1.5)	7.6 ± 1.2
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.00 (0.94 – 1.07)	-	-
CV (%)	5	5	12.2	-	-

$AUC_{0-\infty}$ 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 levetiracetam under fasted conditions, it can be concluded that DRETACEN 1000 mg and Keppra 1000 mg are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Levetiracetam may be taken without reference to food intake. From the literature it is known that food does not alter the extent of absorption of levetiracetam. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1 Guideline on the Investigation of Bioequivalence.

Extrapolation to different strengths
A biowaiver has been granted for the lower strengths, as the following conditions are fulfilled:
- the pharmaceutical products are manufactured by the same manufacturer and process,
- the pharmacokinetics has been shown to be linear over the therapeutic range,

- the composition of the different strengths is dose proportional,
- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the biobatch.

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

Levetiracetam was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levetiracetam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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.

Pharmacovigilance

The innovator product Keppra currently has a one-year PSUR cycle. Therefore, the MAH agreed to follow a one-year PSUR cycle upon approval for Levetiracetam. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, which is in correspondence with the agreed PSUR cycle of the innovator product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the centralised reference product Keppra (EMEA/H/C/000277) except for the product specific particulars.

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. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. A total number of 19 questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

The results of the user testing are acceptable according to the guideline on the readability, because the criterion “90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it” is fulfilled. The package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

DRETACEN 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Keppra 250, 500, 750 and 1000 mg film-coated tablets. Keppra 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement.

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 DRETACEN 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 August 2011. The product was authorised in the Netherlands on 21 September 2011.

The date for the first renewal will be: 29 August 2016.

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

Quality - medicinal product

- The MAH committed to continue the long-term stability study according to the protocol.
- The MAH committed to place at least one commercial batch per strength packaged in marketed container closure size of final packaged product on long-term stability program each year.

Pharmacovigilance

- The MAH committed to follow the one-year PSUR cycle for Levetiracetam Keppra. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, which is in correspondence with the agreed PSUR cycle of the innovator product.

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