CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# TRUND 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets PharOS - Pharmaceutical Oriented Services Ltd., Greece

# 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/2180/001-004/DC**
**Registration number in the Netherlands: RVG 108512-108515**

**23 March 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: | 8 February 2012 |
| Concerned Member States: | Decentralised procedure with HU, PL, CZ, SK, RO, BG |
| 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 TRUND 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets from PharOS - Pharmaceutical Oriented Services Ltd. The date of authorisation was on 8 February 2012 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Keppra 1000 mg film-coated tablets, registered in the EEA and obtained from the Greek 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 or almost white powder, which is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. Levetiracetam has one chiral center and the S-enantiomer is produced. The drug substance has three polymorphic forms. Form I is consistently produced.

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
A flow chart and a brief description of the manufacturing process, including all reagents and solvents have been presented. The information on the manufacturing process is deemed acceptable.

Quality control of drug substance
The drug substance specification is based on the requirements described in the Ph.Eur. monograph of Levetiracetam with additional in-house tests for residual solvents, polymorphism by XRD, particle size and microbiological quality. The limits are in line with or more stringent than described in the monograph and therefore acceptable. The limits for residual solvents are in line with the ICH guidance and the microbial limits are in line with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches of production scale.

Stability of drug substance
Stability data on the active substance have been provided for four batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The stability results show that, other than a slight increase in water content, 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 36 months is justified. The drug substance does not require specific storage conditions.

** 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
TRUND is formulated as a film-coated tablet containing 250 mg, 500 mg, 750 mg or 1000 mg Levetiracetam. The drug products are described as blue (250 mg), yellow (500 mg), orange (750 mg) or white (1000 mg) coloured, oval shaped film-coated tablets with a break line on one side.
The tablets can be divided into equal halves

The MAH confirmed that the breakability of the tablets per strength has been demonstrated according Ph.Eur monograph 0478.

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

The excipients are:
*Core* - crospovidone (Type B), povidone K30, silica colloidal anhydrous, magnesium stearate
*Coating* - hypromellose, macrogol / PEG 400, titanium dioxide (E171), purified talc; indigo carmine Aluminium Lake (E132) (250 mg); iron oxide yellow (E172) (500 mg); sunset yellow Aluminium Lake (E110), iron oxide red (E172) (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 dose proportional to the highest strength. Wet granulation was chosen 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. Comparative dissolution profiles have been presented for the 1000 mg strength of the proposed drug product against the reference product (1000 mg) and the lower strengths of the proposed drug product. At three pH values and for all strengths more than 85% was dissolved after 15 minutes. For the 250 mg, 500 mg and 750 mg strengths of the proposed drug product, comparative dissolution profiles against the 1000 mg strength have also been presented, demonstrating fast full dissolution under all conditions (more than 85% in 15 minutes).
From a chemical-pharmaceutical point of view, the biowaiver for the lower strengths can be accepted. The subdivision of tablets has been adequately demonstrated in compliance with Ph.Eur. requirements. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process for includes steps of granulation, blending, compression and coating of the tablet cores. It concerns a standard manufacturing process.
The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four batches of granulate and three pilot-scale batches per strength for the tablets.

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

Quality control of drug product
Specifications have been presented for the granules and the film-coated tablets. The release and shelf-life specification differ in total impurities for the granules and in water content and total impurities for the tablets. The granules are tested on description, identification of levetiracetam, related substances, water content, assay, chiral impurity and microbial contamination.
The final drug product specification includes tests for description, identification of levetiracetam and enantiomer, dimensions, disintegration, assay, chiral impurity, related substances, uniformity of dosage units by mass variation, uniformity of mass, average weight, subdivision of tablets, moisture content, dissolution and microbial quality. The release and shelf-life limits for water content and total impurities are not identical, but all other parameters have the same release and shelf life limits. The specification is generally deemed acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for four batches of granules and two pilot-scale plus one lab-scale batches per strength for the film-coated tablets stored in PVC-PE-PVDC/Alu blisters at 25°C/60% RH (up to 24 months), 30°C/75% RH (6 months granules and up to 24 months tablets) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The products demonstrate an increase in water content. This trend decreases with lower temperature and humidity conditions. No changes in any of the other parameters were observed. The intermediate and final drug products are demonstrated to be photostable.
The proposed shelf life of 36 months can be granted for the tablets packed in PVC-PE-PVDC/Alu blisters without any specific storage conditions.

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

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 TRUND 1000 mg film-coated tablets (PharOS - Pharmaceutical Oriented Services Ltd, Greece) are compared with the pharmacokinetic profile of the reference product Keppra (UCB Pharma SA, Belgium), obtained from Greece. Besides, both products were compared to the innovator product registered in Australia. Only the Greek reference product is considered relevant for this application, as the Australian reference product is not registered in the EEA. Therefore, only the data of the Greek reference product were used for assessment.

*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 or with the EU reference product.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Design*
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 18 healthy subjects (7 females/11 males), aged 28-55 years. Each subject received a single dose (1000 mg) of one of the 3 levetiracetam formulations. The tablet was orally administered after an overnight fast. Subjects were served a controlled meal not less than 4 hours post-dose, and controlled meals at appropriate times thereafter, in each period. With the exception of the volume administered at the time of dosing, fluids were not permitted from 1 hour before

dosing to 1 hour after dosing, but water was permitted *ad libitum* at all other times. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

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

*Results*
All 18 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 levetiracetam under fasted conditions.

| **Treatment N=18** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 289 ± 40 | 299 ± 43 | 38.6 ± 10 | 0.52 ± 0.29 (0.25 – 2.00) | 7.3 ± 0.8 |
| **Reference** | 293 ± 43 | 303 ± 46 | 41.4 ± 10 | 0.50 ± 0.14 (0.25 – 1.50) | 7.3 ± 0.8 |
| ***Ratio (90% CI)** | 0.99 (0.97-1.10) | 0.99 (0.97-1.00) | 0.93 (0.84-1.03) | -- | -- |
| **CV (%)** | 2.7 | 2.8 | 18.5 | -- | -- |

**$AUC_{0-\infty}$** 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 TRUND 1000 mg and Keppra 1000 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil 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 Note for Guidance on the investigation of bioavailability and 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 manufacturing process,
- the qualitative composition of the different strengths is the same,
- 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),

- appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

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).

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 TRUND. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old, which is in correspondence with the agreed PSUR cycle of the innovator product.

The MAH committed to continue to monitor the following events: abnormal behaviour, blood dyscrasias, seizure worsening, long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children and safety in patients with different epilepsy syndromes younger than 12 months. In addition, the impact of levetiracetam on the teeth in children of this age group should be carefully monitored in post marketing

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.

**Product information**

SPC

The content of the SPC approved during the decentralised procedure is in line with the SPC for the innovator product.

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 three professionals, followed by two rounds with 10 participants each. Eighteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The leaflet scored 100.0% for locating the information necessary to answer the questions very easily or easily and 100.0% for understanding of this information. With these scores, the formal success criteria are met. Therefore, this readability test is considered acceptable.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

TRUND 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.

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 TRUND 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 24 August 2011. TRUND 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets were authorised in the Netherlands on 8 February 2012.

Six-monthly specific safety reports for children < 4 years old should be submitted conform the data lock point for the innovator product.

The date for the first renewal will be: 24 August 2016.

There were no post-approval commitments made during the procedure.

## 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 |
|---|---|---|---|---|---|---|
| | | | | | | |