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Public Assessment Report

Name of the Product:

Levetiracetam PharOS
1500 mg film-coated tablets

(levetiracetam)

Procedure number: HU/H/0523/001/DC

Marketing authorisation holder: Pharmaceutical Oriented Services Ltd.

Date: 11 February 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Levetiracetam PharOS 1500 mg film-coated tablets. The holder of the marketing authorisation is Pharmaceutical Oriented Services Ltd., Greece.

The active substance of Levetiracetam PharOS 1500 mg film-coated tablets (further on: Levetiracetam PharOS) is levetiracetam. One tablet contains 1500 mg of levetiracetam.

The other ingredients are:
- tablet core: crospovidone Type A, crospovidone Type B, povidone, silica, colloidal anhydrous, magnesium stearate;
- film-coating: hypromellose, titanium dioxide (E171), talc, macrogol, iron oxide yellow (E172), indigo carmine aluminium lake (E132).

Levetiracetam PharOS is green, oval shaped, film-coated tablet, scored on one side.

The tablets are available in Aluminium-PVC/PE/PVDC blisters packs supplied in cardboard boxes.

Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Levetiracetam PharOS is used:
- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- As an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents and children above 6 years of age,
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy,
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

What Patients need to know before taking Levetiracetam PharOS

Those who you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine, should not take this medicine,

Warnings and precautions

Patients should talk to their doctor before taking Levetiracetam PharOS
- if they suffer from kidney problems. They should follow the doctor's instructions. He/she may decide if the dose should be adjusted;
- if noticing any slow down in the growth or unexpected puberty development of a child-patient, the doctor should be contacted;
- a small number of people being treated with anti-epileptics such as Levetiracetam PharOS have had thoughts of harming or killing themselves. If the patient has any symptoms of depression and/or suicidal ideation, the doctor should be contacted.

Children and adolescents

Levetiracetam PharOS is not indicated in children and adolescents below 16 years on its own (monotherapy) or any weighing less than 50 kg.

Other medicines and Levetiracetam PharOS

Patients should inform their doctor if taking, have recently taken or might take any other medicines.

They should not take macrogol (a medicine used as laxative) for one hour before and one hour after taking levetiracetam as this may results in a reduction of its effect.

Pregnancy and breast-feeding

Those who are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby, consult their doctor for advice before taking this medicine. Levetiracetam can be used during pregnancy, only when, after careful assessment, it is considered necessary by the doctor. A risk of birth defects for the unborn child cannot be completely excluded.

The patient should not stop the treatment without discussing this with the doctor.

Breast-feeding is not recommended during treatment.

Driving and using machines

Levetiracetam PharOS may impair the ability to drive or operate any tools or machinery, as it may make the patient feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. Patients should not drive or use machines until it is established that his/her ability to perform such activities is not affected.

How to take Levetiracetam PharOS

Patients should take the number of tablets following their doctor's instructions.

Levetiracetam PharOS must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Levetiracetam PharOS is not suitable for therapy initiation, for dose adjustments or for gradually withdrawal. Levetiracetam PharOS is not available in all pharmaceutical forms described below. For these dosages and pharmaceutical forms, particularly for starting dose and dose adjustments other medicinal products containing levetiracetam should be used.

Monotherapy

Dose in adults and adolescents (from 16 years of age):
- general dose: between 1000 mg and 3,000 mg each day;
- when they will first start taking Levetiracetam PharOS, the doctor will prescribe a lower dose during 2 weeks before giving the patient the lowest general dose.
  Example: if the patient's daily dose is 1000 mg, the reduced starting dose is 2 tablets of 250 mg in the morning and 2 tablets of 250 mg in the evening.

Add-on therapy

Dose in adults and adolescents (12 to 17 years) weighing 50 kg or more:
- general dose: between 1,000 mg and 3,000 mg each day.
  Example: if the daily dose is 1,000 mg, the patient might take 2 tablets of 250 mg in the morning and 2 tablets of 250 mg in the evening.
- Dose in children (6 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg: Levetiracetam PharOS 1500 mg tablets are not suitable for the treatment of children and adolescents weighing less than 50 kg.

Method of administration

Patients should swallow the tablets with a sufficient quantity of liquid (e.g. a glass of water).

Levetiracetam PharOS may be taken with or without food.

The tablets can be divided into two equal doses.

Duration of treatment

Levetiracetam PharOS is used as a chronic treatment. Patients should continue the treatment for as long as their doctor has told them. They should not stop the treatment without the doctor's advice as this could increase their seizures.

What to do if more Levetiracetam PharOS has been taken than it should have been?

The possible side effects of an overdose of Levetiracetam PharOS are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.
In this case the doctor must be contacted. The doctor will establish the best possible treatment of overdose.

What to do if taking Levetiracetam PharOS has been forgotten?

The doctor should be contacted if one or more doses have been missed. Patients should not take a double dose to make up for a forgotten dose.

May taking Levetiracetam PharOS be stopped?

If stopping treatment, Levetiracetam PharOS should be discontinued gradually to avoid an increase of seizures. When the doctor decides to stop the Levetiracetam PharOS treatment, he/she will instruct the patient about the gradual withdrawal.

Possible side effects

Like all medicines, Levetiracetam PharOS can cause side effects, although not everybody experiences them.

Patients must tell their doctor immediately, or go to the nearest emergency department, if experiencing:
- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction;
- swelling of the face, lips, tongue and throat (Quincke's oedema);
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]);
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function;
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme);
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome);
- a more severe form of rash causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis);
- signs of serious mental changes or if someone around the patient notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported adverse reactions were nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase

side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

Very common (may affect more than 1 in 10 people) side effects:
- nasopharyngitis;
- somnolence (sleepiness), headache.

Common (may affect up to 1 in 10 people):
- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

Uncommon (may affect up to 1 in 100 people):
- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain);
- injury.

Rare (may affect up to 1 10 1000 people):
- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function;

- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis);
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non- Japanese patients;
- limp or difficulty walking.

How to store Levetiracetam PharOS

This medicine does not require any special storage conditions but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Levetiracetam PharOS 1500 mg film-coated tablets. The procedure was finalised at 4 July 2018. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use,* an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: France) concerned a hybrid application of levetiracetam 1500 mg film-coated tablets (Levetiracetam PharOS Health tablets).

The active substance of the above-mentioned medicinal products, levetiracetam, has been in medicinal use within the Community for more than ten years, with recognized efficacy and an acceptable level of safety. Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets are authorised for marketing in the European countries under the brand name Keppra®, marketed by UCB Pharma S.A., Belgium. Keppra has been centrally authorized in the European community since 2000.

The concerned 1500 mg levetiracetam strength was submitted by PharOS Pharmaceutical Oriented Services Ltd. with the aim of obtaining generic levetiracetam 1500 mg film-coated tablets that are *in vitro* and *in vivo* equivalent to two tablets of the 750 mg strength of the innovator brand Keppra.

The essential similarity between the reference product and Levetiracetam PharOS 1500 mg film-coated tablets has been shown through a bioequivalence study, therefore, except for showing bioequivalence the application contained no new non-clinical or clinical data, other than supporting literature where necessary.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Levetiracetam PharOS 1500 mg film-coated tablets. The authorisation has been issued pursuant to Article 10(3) pf the Directive 2001/83/EC.

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 and as adjunctive therapy in:

- treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
- treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- 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 Summary of Product Characteristics.

II. QUALITY ASPECTS

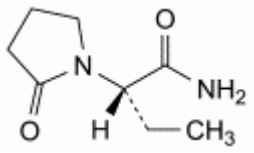
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Levetiracetam PharOS 1500 mg film-coated tablets via a decentralized procedure according to Article 10(3) of Directive 2001/83/EC (hybrid application). The product has been submitted by PharOS Pharmaceutical Oriented Services Ltd. The reference product was Keppra® a film-coated tablet containing 250, 500, 750 and 1000 mg of Levetiracetam. The innovator product is marketed in Europe by UCB Pharma S.A., Belgium.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of suitability (CEP) procedure in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non-proprietary name (INN): levetiracetam
Ph. Eur. monograph No.: 01/2017:2535
Chemical name: (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide
Structure:



The drug substance is a white to almost white powder. It is very soluble in water, soluble in acetonitrile, practically insoluble in hexane.

All aspects of the manufacture and control of the drug substance are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) CEP.

The drug substance has been specified according to the requirements of the current Ph. Eur. monograph on levetiracetam with additional requirements stated on the CEPs.

The test procedures are performed in accordance with the Ph. Eur. monograph on levetiracetam. Tests for residual solvents are performed in accordance with the annex of the valid CEP.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered bioequivalent products to the reference product Keppra film coated tablets containing the same amount of the drug substance (two tablets of 750 mg strength). A satisfactory account of the pharmaceutical development has been provided.

Comparable *in vitro* dissolution profiles have been provided for the test and reference products. As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies, a product with the following appearance and composition was obtained: green, oval shaped, film-coated tablets, scored on one side. The dimensions of the tablets are 21.6 mm x 11.4 mm ± 5 %. The film-coated tablets can be divided into equal doses.

The excipients included in the tablet core are crospovidone, povidone, and silica colloidal anhydrous and magnesium stearate. The film-coating consists of hypromellose, titanium dioxide, macrogol, talc and colouring agents (iron oxide yellow and indigo carmine aluminium lake).

All excipients used in the manufacturing comply with respective Ph. Eur. monographs, except for the colouring substances of coating material (Iron oxide yellow (E172) and Indigo carmine aluminium lake (E132). However, these components comply with EU Regulation No. 231/2012.

Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and

complied with the specification. Certificates of analysis for the batches involved in the bioequivalence studies are presented.

Levetiracetam PharOS 1500 mg film-coated tablets are packed in Aluminium-PVC/PE/PVDC blisters. The PVC/PE/PVDC forming foil consists of a polyethylene (PE) layer coated with a polyvinyl chloride (PVC) film on one side and polyvinylidene chloride (PVDC) on the other side, having a total thickness of 328 μm + 5% sealed against an aluminium sealing foil. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 36 months is approved with the following storage condition: "This medicinal product does not require any special storage conditions".
.
The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Levetiracetam PharOS 1500 mg film-coated tablets have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view, the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well known. As levetiracetam is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, levetiracetam. An overview based on literature review is appropriate for this kind of submissions.

III.2 Pharmacology

The drug product Levetiracetam PhaOS 1500 mg film-coated tablets contains the active substance levetiracetam, which is a pyrrolidone derivate. Its mechanism of action remains to be fully elucidated. Although the precise mechanism is unknown, levetiracetam has been shown to bind to synaptic vesicle protein 2A, a protein involved in the coordination of synaptic vesicle exocytosis and neurotransmitter release. The interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of the drug. Levetiracetam also has been found to selectively inhibit N-type Ca2+ channels, activate GABA current and possess novel desynchronizing effect on neurons that might be involved in the molecular basis of epilepsy. Anti-epileptogenic effects of levetiracetam in addition to anticonvulsive effects have been reported in the rat amygdala kindling model for temporal lobe epilepsy and the spontaneously epileptic rat, a model of primary generalized epilepsy characterized by spontaneous tonic convulsions and absence seizures.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant and further studies are not required.

III.4 Toxicology

Published information on toxicological studies with levetiracetam was the basis for the evaluation. No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment

The product submitted for marketing authorization is a hybrid product that will be used interchangeably with other similar products already have been marketed in Europe. The introduc-

tion of this product onto the market is unlikely to result in any significant increase in the combined sales volumes for all levetiracetam products, thus would not be expected to have an adverse effect upon the environment. For this reason, no formal environmental risk assessment is considered to be necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of levetiracetam are well-known. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Except for demonstrating bioequivalence no new clinical studies were conducted by the applicant as the application is submitted in accordance with Article 10(3) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %. Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively. The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans. Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of levetiracetam with other substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose.

The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.

The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

IV.2.2 Bioequivalence study

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Results of comparative dissolution tests of Levetiracetam PharOS 1500 mg film-coated tablets and the reference product Keppra 750 mg film-coated tablets performed in 0.1 M HCl as well as at pH 4.5 and 6.8 dissolution media could be accepted as similar, since more than 85% of levetiracetam was dissolved in 15 minutes according to the requirements of the bioequivalence guideline in force (CPMP/EWP/QWP/EWP/ 1401/98 Rev. 1/ Corr **).

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product and reference product. This single dose, crossover study was performed in order to support essential similarity between the test product Levetiracetam 1500 mg film-coated tablets (for PharOS, Greece), one tablet and Keppra® (levetiracetam) film-coated tablets 750 mg (manufactured by UCB Pharma SA, Brussels, Belgium, Reference) at a dose of 1500 mg (2 tablets of 750 mg). The study involved healthy adult, male subjects under fasting conditions according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/ Rev 1/Corr** 2010). Its main objective was to compare the rate and extent of absorption of the Test- and Reference products administered to healthy volunteers in a single dose under fasting condition.

The tablets had to be swallowed whole, not be chewed, crushed or divided with approximately 240 ml of room temperature water.

Blood samples were taken at appropriate time-periods. They were extracted then and analysed using UPLC-ESI-MS/MS method.

Results of incurred samples reanalysis and analytical method validations fulfilled all acceptance criteria according to the *Guideline on bioanalytical method validation* (EMEA/CHMP/EWP/192217/2009, 21 July 2011).

The study was conducted in compliance with the study protocols and requirements of *guideline on Good Clinical Practice* (CPMP/ICH/135/95), *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP /1401/98) and ethical principles stated of the latest version of Declaration of Helsinki.

The most important statistical methods used in the evaluation were as follows:

- descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for test- and reference pharmacokinetic data;
  log-transformation of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} data;
- calculation of 90% confidence intervals for the difference between the least square means for primary parameters;
- applying non-parametric analysis of T_{max} on untransformed data;
- descriptive statistics of safety data collected during the whole study period.

Bioequivalence criteria: the ratio of geometric means with corresponding 90% confidence intervals calculated from the exponential of the difference between the Test- and Reference products for the ln-transformed parameters C_{max} and $AUC_{0\text{-}t}$ should be within the 80.00 to 125.00% range.

The Table below shows that the bioequivalence criteria were met. The results support that a single dose (1 tablet of 1500 mg) of Test product is bioequivalent with a single dose of Reference product (2 tablets of 750 mg) in healthy adult subjects under fasting condition.

Pharmacokinetic parameter	Ratio (T/R)	90% Confidence interval	CV %
C_{max}	97.53	91.63 – 103.81	12.9
AUC_{0-t}	99.93	97.67 – 101.03	3.49
$AUC_{0-\infty}$	99.87	98.55 – 101.20	2.74

Safety: no death, serious or clinically significant adverse events occurred during the study. The Test- and Reference product were comparable in their safety and tolerability. Overall, the drugs investigated were well tolerated by subjects included in the study. No new safety concern was identified.

IV.3 Pharmacodynamics

No clinical pharmacology studies were performed to evaluate the pharmacodynamics of Levetiracetam PharOS 1500 mg film-coated tablets and none are required for the applications of this type.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of levetiracetam.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of levetiracetam.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Abnormal behaviour Suicidality Blood dyscrasias
Important potential risks	Seizure worsening Medication error
Missing information	Use during pregnancy (including deterioration of seizure control during pregnancy) Decreased bone mineral density after prolonged exposure

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Levetiracetam PharOS 1500 mg film-coated tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Levetiracetam PharOS 1500 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The hybrid application concerned Levetiracetam PharOS 1500 mg film-tablets.

Abridged applications avoid the need for repetitive tests on humans. For these applications the bioequivalence studies described in section IV.2 are pivotal.

To support the request, the applicant has adequately demonstrated bioequivalence between one Levetiracetam PharOS 1500 mg film-coated tablet and two tablets of Keppra 750 mg film-coated tablets.

There are no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concerns Levetiracetam PharOS 1500 mg film-coated tablets, hybrid version of levetiracetam. The holder of the marketing authorisation is Pharmaceutical Oriented Services Ltd., Greece.

The approved indication is monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy and as adjunctive therapy in:

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

The application was submitted according to Article 10(3) of Directive 2001/83/EC (hybrid application). The reference product was Keppra®, marketed by UCB Pharma S.A., Belgium (two 750 mg tablets). The applicant has adequately proven bioequivalence between the test and reference products.

The application contains an adequate review of published clinical data. Moreover, similarity with the reference product based on pharmaceutical attributes has been shown.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Levetiracetam PharOS 1500 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

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 language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached