London, 19 May 2011
EMA/457042/2011
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Levetiracetam Teva

International non proprietary name: levetiracetam

Procedure No. EMEA/H/C/002316

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Teva Pharma B.V. submitted on 1 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam Teva, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 March 2010.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC, as amended.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The applicant applied for the following indication: Levetiracetam Teva 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.

Levetiracetam Teva 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.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Keppra instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: **Keppra 250 mg, 500 mg, 750 mg, 1000 mg film-coated tablets**
- Marketing authorisation holder: **UCB Pharma SA**
- Date of authorisation: **29-09-2000**
- Marketing authorisation granted by: Community
- Marketing authorisation numbers: **EU/1/00/146/006 - EU/1/00/146/013**

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: **Keppra 250 mg, 500 mg, 750 mg, 1000 mg film-coated tablets**
- Marketing authorisation holder: **UCB Pharma SA**
- Date of authorisation: **29-09-2000**
- Marketing authorisation granted by: **Community**

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: **Keppra 500 mg, 1000 mg film-coated tablets**
- Marketing authorisation holder: **UCB Pharma SA**
- Date of authorisation: **29-09-2000**
- Marketing authorisation granted by: **Community**
- Marketing authorisation number(s): **EU/1/00/146/006 - EU/1/00/146/013, EU/1/00/146/020 - EU/1/00/146/026**

The Rapporteur appointed by the CHMP was:

Rapporteur: **Pierre Demolis**

### *Scientific Advice*

The applicant did not seek scientific advice at the CHMP.

### *Licensing status*

The product was not licensed in any country at the time of submission of the application.

## *1.2. Steps taken for the assessment of the product*

- The application was received by the EMA on 1 October 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 January 2011.
- During the meeting on 14-17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 May 2011.
- During the meeting on 16-19 May 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Levetiracetam Teva on 19 May 2011.

# 2. Scientific discussion

## *2.1. Introduction*

Levetiracetam Teva tablets is a generic medicinal product containing the active substance levetiracetam.

The reference medicinal product is Keppra film-coated tablets authorised on 29 September 2000.

Levetiracetam is a chemical entity related to piracetam, a nootropic drug. Initial research was directed primarily towards indications where piracetam and piracetam-like compounds had shown to be of potential benefit (cognition, anxiety disorders). When the particular antiepileptic profile of the drug was recognised, its development was oriented towards epilepsy as a new indication in 1991.

The precise mechanism of action by which levetiracetam confers seizure protection is unknown, but it appears to be unrelated to the mechanisms identified for current antiepileptic drugs.

Levetiracetam is indicated for the treatment of Epilepsy.

The efficacy and safety of levetiracetam has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Keppra.

Bioequivalence to the reference product was demonstrated by two bioequivalence studies at single dose under fasting conditions. The studies were performed in healthy volunteers. One study was performed with the 500 mg strength tablet and the second with the 1000 mg tablets.

The indication proposed for Levetiracetam Teva is identical to the indication of the reference medicinal product.

The therapeutic indication of Levetiracetam Teva is:

- 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.
- 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.

## *2.2. Quality aspects*

### 2.2.1. Introduction

Levetiracetam Teva 250 mg, 500 mg, 750 mg and 1000 mg are presented as oblong shaped immediate-release film-coated tablets which differ from each other in mass, colour (250 mg: blue, 500 mg: yellow, 750 mg: orange, 1000 mg: white), and marking.

They contain 250 mg, 500 mg, 750 mg and 1000 mg of Levetiracetam as drug substance, respectively. The four strengths are strictly homothetic.

The formulation comprises the following excipients: maize starch, povidone, croscarmellose sodium, magnesium stearate, and opadry as coating agent.

The medicinal product is packaged in PVC/PVdC-Aluminium foil blisters of 30, 50, 50x1, 60, 100, 120 and 200 film-coated tablets.

## 2.2.2. Active Substance

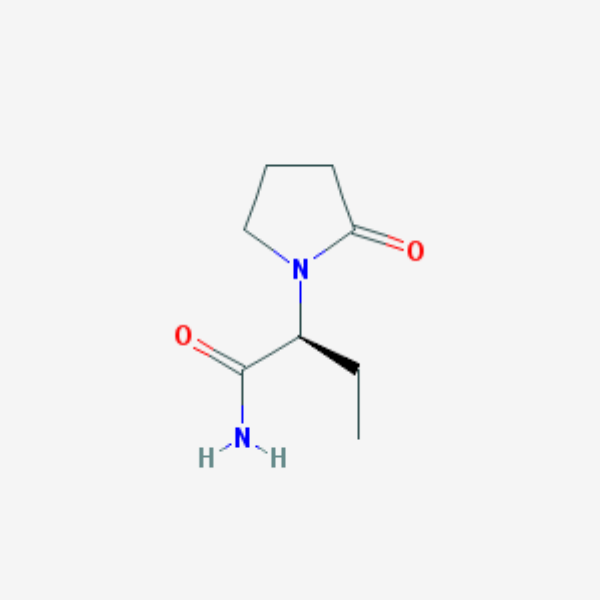


Figure 1: Chemical structure of levetiracetam

Levetiracetam is a white to off-white crystalline powder very soluble in water. It is also freely soluble in chloroform and in methanol, soluble in ethanol, sparingly soluble in acetonitrile, and insoluble in n-hexane. It is slightly hygroscopic and presents one single asymmetric centre, leading to 2 optical isomers, where the active is the S-enantiomer. According to the synthetic process described in this application the active substance is consistently obtained as the S-enantiomer and is routinely controlled with an enantiomeric purity test.

Levetiracetam does not present polymorphism. The same polymorphic form is obtained (demonstrated by XRD). Stability of the form has been studied under high temperature and pressure conditions.

### *Manufacture*

The Active Substance Master File (ASMF) procedure was followed for the active substance. Letter of access has been received from the ASMF Holder. Levetiracetam is manufactured in two manufacturing sites.

The active substance is synthesised in two steps, the first step involving chemical reaction followed by a crystallization step.

Full description of the manufacturing was provided in the restricted part of the ASMF.

Confirmation of the chemical structure of levetiracetam was provided by elemental analysis, IR spectroscopy, 1H-NMR and C13-NMR, and mass spectrometry.

### *Specification*

Levetiracetam is described in the last edition of the European Pharmacopoeia (Ph. Eur.). The Ph. Eur. monograph specifications have been implemented by both active substance and finished product manufacturers, where applicable, to control of the active substance. The specification also complies with ICH Q3A and includes tests for appearance (visual), identification (HPLC, IR), assay (HPLC), related substances (HPLC), heavy metals, sulphated ash, water content, chiral purity (specific optical rotation), and residual solvents. Particle size distribution (Laser Diffraction) and density are additional

specification tests implemented by the finished product manufacturer. In-house analytical procedures have been described and validated.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Two batches from each manufacturing site have been submitted. Results demonstrate compliance to the proposed limits and are consistent between batches and between manufacturing sites.

### *Stability*

Stability studies were performed on 12 batches from both manufacturing sites for a total duration of up to 60 months at long-term conditions (25°C/60%RH) and accelerated conditions (40°C/75%RH).

The data submitted support the re-test period proposed.

## 2.2.3. Finished Medicinal Product

### *Pharmaceutical Development*

The aim was to develop an immediate-release, conventional tablet with a relatively rapid drug release similar to that of the reference product Keppra.

A common formulation and manufacturing process was developed for Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets.

The selected manufacturing process comprises standard wet granulation followed by compression and film-coating.

Excipients used in the formulation were all compendial, well known and widely used for this dosage form. The excipients used include: maize starch, povidone, croscarmellose sodium, magnesium stearate, and opadry as coating coating agent. The Opadry components are of compendial quality (hypromellose, titanium dioxide, macrogol) and controlled by in-house specifications (colour agents).

Container closure system consists of PVC/PVdC-Aluminium foil blister and is in line with current regulatory requirements.

In vitro dissolution studies were conducted in different media and met the $F_2$ requirements.

Levetiracetam 500mg was used in the bioequivalence study versus reference product Keppra 500mg and Levetiracetam 1000mg was used in the bioequivalence study versus reference product Keppra 1000mg.

Additional strengths of the product series, 250mg and 750mg, have not been tested in vivo for bioequivalence. Exemption of a bioavailability study for the 250 mg and 750 mg strengths was acceptable since all requirements of a biowavier for these strengths have been fulfilled.

### *Adventitious agents*

All excipients used comply with the provisions of Commission Directive 2001/83/EC as amended and with Chapter 5.2.8. "Minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" of the Ph. Eur.

BSE/TSE Statements for the excipients are provided and are acceptable. The products do not contain and are not derived from any category A or B as defined in the TSE guideline (EMEA/410/01 rev.2).

## *Manufacture of the product*

The manufacturing process for film-coated tablets can be summarized in nine steps and can be considered as standard: pre-mixing, wet granulation, drying, milling, blending with croscarmellose sodium, and final blending with magnesium stearate, compression, coating and packaging.

The manufacturing process has been adequately described and the critical steps have been identified. An adequate flow-chart was provided and the different steps of the manufacturing process are described, together with equipment type and operating parameters.

The manufacturing process has been satisfactorily validated at pilot scale. The results demonstrate content homogeneity and reproducibility of the blends. The compression step has been correctly validated. All tests performed throughout the compression run comply with specifications. The influence of hardness on dissolution was verified at low hardness, high hardness and target hardness during the manufacture of pilot batches. The stressed conditions for hardness were achieved by compressing close to the upper and lower specification limits. They demonstrate that hardness has no impact on the dissolution whatever the tablet strength. The coating is validated by dissolution test. The validation results demonstrate batch-to-batch consistency. The analytical results are consistent and comply with the proposed drug product specification.

The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

## *Product Specification*

Adequate release and shelf-life specification have been presented for the finished product and include: Appearance (visual examination), Identification (HPLC, IR), Dissolution (Ph. Eur.), Uniformity of dosage units (Ph. Eur.), Assay (HPLC), Impurities and degradation products (HPLC), Microbial test (Ph. Eur.), Water content (Karl Fischer) and Identification of colorants (HPLC). Limits are in line with current guidelines. Analytical procedures are described and validated.

Batch data has been provided for two pilot scale tablet batches of each of the four strengths (including the biobatches). Batch analysis results are conforming to specifications.

## *Stability of the product*

Stability studies under ICH long-term and accelerated conditions (i.e. 25°C/60% RH and 40°C/75% RH) have been carried out on two pilot batches of each strength (250 mg, 500 mg, 750 mg and 1000 mg).

The results of the following tests were submitted: appearance, assay and related substances, dissolution, microbial testing, and water content.

The analytical methods used for the stability studies are identical with the methods proposed for routine testing of the finished product. The methods for assay and related substances were proven during their validations as stability-indicating.

During the stability studies the product did not show any significant change in the quality. All the results remained well within the specification limits during all the stability studies. Results for bulk stability studies of all strengths were also acceptable.

Based on the stability data, the proposed shelf life of the finished product in the packaging described of 3 years can be accepted without special storage conditions.

### 2.2.4. Discussion on chemical, and pharmaceutical aspects

Levetiracetam is described in the last edition of the European Pharmacopoeia. Where applicable, specifications applied by the active substance and the finished product manufacturers are in-line with the monograph.

The pharmaceutical development of the formulation and the manufacturing process have been satisfactorily documented. Bioequivalence studies were performed on the test product Levetiracetam Teva 500 mg tablet versus the reference product Keppra 500 mg tablet, and on the test product Levetiracetam Teva 1000 mg tablet versus the reference product Keppra 1000 mg tablet. Additionally, comparative in vitro dissolution profiles of the test products (including additional strengths not tested for bioequivalence) and the reference products were provided to support the essential similar character.

The manufacturing process was described and the critical steps identified. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process was adequately validated at pilot scale at the proposed manufacturing site.

The routine specifications and tests methods proposed for the drug product will adequately control the quality of the product. Analytical methods were well described and validated in agreement with ICH guidelines.

Batch analyses were presented and the results showed that the drug product meets the specifications proposed.

The container-closure systems consisting of PVC/PVdC-Aluminium foil blister was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for drug product were adequately established.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

## *2.3. Non- Clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

### 2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Levetiracetam Teva manufactured by Teva Pharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all levetiracetam containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased. The CHMP agreed with the applicant's justification for not providing an ERA.

## *2.4. Clinical Aspects*

### 2.4.1. Introduction

This is an abridged application for tablets containing Levetiracetam. To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting conditions. These studies were the pivotal studies for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of levetiracetam based on published literature; this was considered acceptable. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that the clinical trials conducted were carried out in accordance with the ethical standards.

To support this application, the applicant submitted two bioequivalence studies. One study was performed with the 500 mg strength tablet and the second with the 1000 mg tablets.

With both strengths, the bioequivalence of the generic products to adequate comparators has been tested at single dose under fasting conditions.

The studies were performed in healthy volunteers.

According to the applicant these studies were conducted in accordance with the guidelines set forth by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH Guideline E6), the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (21 CRF Parts 50 and 56) and the Declaration of Helsinki regarding the treatment of human subjects in a study.

Inspections by Health Authorities had positive outcomes and confirmed their compliance with GCP and GLP.

### *Exemption*

Four different strengths of Levetiracetam tablets (250 mg, 500 mg, 750 mg, 1000 mg) have been developed by the MAH. The application for all the dosage strengths is based on two bioequivalence studies with Levetiracetam Teva 500 mg and 1000 mg film-coated tablets.

This is considered acceptable as all the conditions from section 4.1.6. of the "Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1" are fulfilled.

## 2.4.2. Pharmacokinetics

To support the application, the applicant has submitted two bioequivalence studies:

- The study investigating the 1000 mg strength is a single dose (under fasting conditions) trial.
- The study investigating the 500 mg strength is a single dose (under fasting conditions) trial.

**Study investigating the 1000 mg strength**

**Study design**

The study was an open label, two-treatment, two periods, two sequence, single dose, crossover study conducted under fasting conditions with a wash out period of 7 days between administrations.

A 1000 mg tablet was administered in each period with 240 ml water.

Twenty-one blood samples were collected pre-dosing and up to 36 h post-dosing, in blood collection tubes containing EDTA K2 in each period. Samples assayed for levetiracetam by a validated technique.

The CHMP considered that the design of the study was adequate. The sampling period is considered sufficient to characterize the plasma concentration-time profile and to ensure measurements over a period of at least 5 half-lives of levetiracetam. Blood samples timing was appropriate to allow an accurate measurement of $t_{max}$. The wash-out period of 7 days is long enough to avoid any carry over effect to the second period.

**Test and Reference product**:

Levetiracetam 1000 mg film coated tablets were compared with Keppra 1000 mg film coated tablets.

Levetiracetam 1000 mg film coated tablets were compared with Keppra 1000mg film coated tablets (batch n° 26188), marketed by UCB (Expiry date: August 2009).

The CHMP considered that Keppra tablets were authorised in the EU through the centralized procedure. The reference product is therefore the same in all member states.

Certificates of analysis were enclosed for all the batches used in the bioequivalence studies (generic and reference products). The assayed content of the batches used as test products did not differ more than 5% from that of the batches used as reference products.

The batches of Levetiracetam tablets used for the bioequivalence studies were considered representative of the intended commercial production.

**Population(s) studied**

Based on historical data available, the intra-individual variabilities of AUC and Cmax were estimated to be approximately 12 and 18 %. Expecting ratio of AUC and Cmax within 0.95-1.05 the number of subjects to be included for a 90% powered study was estimated to be 22.

The study sample size was modified to 19 subjects instead of 24 as firstly required by the protocol, this number of subjects was conjointly decided between the CRO and the Sponsor.

Finally, 19 healthy volunteers (6 females and 13 males) were randomised and enrolled into the study. 18 of them completed the entire phases of the study and thus included in the final analysis, as a subject did not show-up for confinement in period 2.

The eighteen (18) individuals who completed both treatment periods were included in the pharmacokinetic analyses with the exception of one subject in Period 2 that had to be excluded from the pharmacokinetic analyses. Therefore, seventeen (17) individuals were included in the pharmacokinetic analyses.

The CHMP considered that acceptable inclusion and exclusion criteria were followed, and that the outcome of the study showed that sufficient number of subjects was included in the study.

**Analytical method**

The blood samples, after a protein precipitation procedure, were analyzed by a validated technique. Analytical procedures are clearly described and a full validation report is provided.

The demonstration of long term stability is adequate as it covers more than the whole period of storage.

The CHMP considered that the analytical method had been satisfactory validated (pre-study and within study) and that its LLOQ allows a suitable investigation the bioavailability of levetiracetam.

**Pharmacokinetic Variables**

Relevant PK parameters of levetiracetam were estimated. The pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$ and $t_{max}$ were either observed or calculated. AUC was calculated by the trapezoidal rule. $C_{max}$ and $t_{max}$ were directly estimated from the individual concentrations:time profiles.

**Statistical methods**

Using GLM procedures in SAS, ANOVA was performed on ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{t/inf}$, and $C_{max}$ and untransformed Kel and $T_{1/2}$ el at the alpha level of 0.05.

A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the $t_{max}$ between treatments.

Ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (A/B) of least-squares means for ln-transformed $AUC_{0-t}$t, AUCinf, and $C_{ma}$ were within the acceptable range of 80% and 125%.

**Bioequivalence criteria**

90% geometric confidence intervals of the ratio (Test/Reference) of least square means from the ANOVA ln-transformed values for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ should be within 80-125%.

The CHMP considered that statistical methods had been adequately described and are acceptable.

**Results**

Levetiracetam Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)

| Treatment | $AUC_{0-t}$ hr.ng/ml | $AUC_{0-\infty}$ hr.ng/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| Test (S.D.) | 255388 (40440) | 263897 (41395) | 30962 (5870) | 0.833 |
| Reference (S.D.) | 258753 (41482) | 267886 (42376) | 32080 (6208) | 0.667 |
| *Ratio (90% CI) Point estimate | [96.27-101.25] 98.73 % | [96.19; 100.92] 98.53 % | [89.43;104.44] 96.65 % | |
| Intra-subject CV (%) | 4.19% | 3.99 % | 12.93 % | |

| | |
|---|---|
| $AUC_{0-\infty}$ | 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 |

**log-transformed values*

**Safety evaluation**

Only a descriptive report of adverse events was provided. No statistical analysis has been performed.

A total of 25 post-dose adverse events were reported by 12 of the 19 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 14 adverse events occurred with treatment A and 11 adverse events with treatment B.

The most commonly reported adverse events were "Dizziness", "Headache", and "Somnolence" each reported by 15.8 % (n=3) of subjects who constituted the safety population. Of the 25 post-dose adverse events reported, 23 were graded as mild and 2 were graded as moderate. Of the 25 post-dose

adverse events reported, the relationship of 4 adverse events was judged as "probably", 14 as "possibly", 6 as "unlikely", and 1 as "unrelated". No serious or significant adverse events were reported during this study. Upon conclusion of the clinical portion of the study, the results from the subjects who completed post-study procedures, including laboratory tests, confirmed the absence of significant changes in the subjects' state of health.

**Study investigating the 500 mg strength**

**Methods**

**Study design**

The study was an open label, two-treatment, two periods, two sequence, single dose, crossover study conducted under fasting conditions with a wash out period of 7 days between administrations.

A 500 mg tablet was administered in each period with 240ml water.

A total of 22 blood samples were collected pre-dosing and up to 36 h post-dosing in each period. All the samples were transferred to the freezer maintained at -65 ± 10 C for final storage until the completion of analysis.

The design of the study was considered adequate by the CHMP. The sampling period of 36 hours is sufficient to characterize the plasma concentration-time profile and to ensure measurements over a period of at least 5 half-lives of levetiracetam and Blood samples timing is appropriate to allow an accurate measurement of $t_{max}$. The wash-out period of 7 days is long enough to avoid any carry over effect to the second period.

**Test and reference products:**

Levetiracetam 500 mg tablets were compared with Keppra 500 mg tablets (batch n° 44814), marketed by UCB (Expiry date: January 2011).

The CHMP noted that Keppra tablets were authorized in the EU through the centralized procedure. The reference product is therefore the same in all member states.

Certificates of analysis are enclosed for all the batches used in the bioequivalence studies (generic and reference products). The assayed content of the batches used as test products did not differ more than 5% from that of the batches used as reference products.

The batches of Levetiracetam tablets used for the bioequivalence studies were considered representative of the intended commercial production.

**Population(s) studied**

Based on sponsor's previous in-house studies, intra-subject variability of 18% for $C_{max}$, sample size computation was done considering following parameters:

T/R ratio=95-105 %

Intra-subject variability C.V. (%) ~18 %

Significance Level = 5 %

Power>80 %

Bioequivalence limits=80.00-125.00 % ($C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$)

Based on the above estimates, a sample size of 22 subjects was sufficient to establish bioequivalence between levetiracetam formulations under fasting conditions with sufficient power.

Thus a total of twenty-six male subjects were checked-in for the trial, and as per the protocol, twenty-four subjects were dosed in Period-I of the trial. In total, twenty-three subjects completed the clinical phase of the trial successfully.

The CHMP considered that acceptable inclusion and exclusion criteria were followed, and that the outcome of the study shows that sufficient number of subjects was included in the study.

**Analytical method**

The blood samples were analyzed for levetiracetam using a validated technique. Analytical procedures are clearly described and a full validation report was provided. An adequate in-study quality control has been performed.

The CHMP considered that the analytical method had been satisfactory validated (pre-study and within study).

Its LLOQ allows a suitable investigation the bioavailability of levetiracetam.

The demonstration of long term stability is adequate as it covers more than the whole period of storage.

**Pharmacokinetic Variables**

The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for Levetiracetam.

Relevant PK parameters of levetiracetam were estimated.

The pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$ and $t_{max}$ were either observed or calculated. AUC was calculated by the trapezoidal rule. $C_{max}$ and $t_{max}$ were directly estimated from the individual concentrations: time profiles.

**Statistical methods**

Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC GLM of SAS® Release 9.1.3 (SAS Institute Inc., USA) to assess the bioequivalence of Levetiracetam.

Descriptive statistics of all pharmacokinetic parameters were computed and reported for Levetiracetam.

ANOVA was performed for the un-transformed and ln-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$.

**Bioequivalence criteria**

90% geometric confidence intervals of the ratio (Test/Reference) of least square means from the ANOVA ln-transformed values for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ should be within 80-125%. $t_{max}$ was tested using a null hypothesis non parametric test (Wilcoxon's Signed-Rank test).

The CHMP considered that the statistical methods have been adequately described and are acceptable.

**Results**

Levetiracetam Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)

| Treatment | $AUC_{0-t}$ hr.ng/ml | $AUC_{0-\infty}$ hr.ng/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| Test (S.D.) | 124594 (15510) | 143978 (20516) | 13890 (2639) | 0.833 |
| Reference (S.D.) | 125378 (16687) | 143859 (21301) | 13807 (2909) | 1 |
| *Ratio (90% CI) Point estimate | [97.42-101.59] 99.5% | [97.85-103.05] 100.4 % | [94.02-108.02] 100.8% | |
| Intra-subject CV (%) | 4.1% | 5 % | 13.7 % | |

$AUC_{0-\infty}$ 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

**log-transformed values*

**Safety evaluation**

A total of 6 post-dose adverse events were reported by 5 subjects who received at least one dose of the study medication (safety population), 4 adverse events occurred with treatment A (test product) and 2 adverse events with treatment B (reference product).

The most commonly reported adverse events were "headache", "cough", "urticaire" and "Dizziness".

**Pharmacokinetic conclusions**

Based on the submitted bioequivalence studies, the following conclusions could be drawn:

The 1000 mg tablet under consideration is bioequivalent to the brand leader (Keppra 1000mg) after single dose under fasting conditions.

The 500 mg tablet under consideration is bioequivalent to the brand leader (Keppra 500mg) after single dose under fasting conditions.

The conclusions of these studies can be extrapolated to the lower strengths 750 mg and 250 mg.

## 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

## 2.4.4. Additional data

Not applicable.

## 2.4.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

## 2.4.6. Discussion on Clinical aspects

Levetiracetam Teva has a well-recognised efficacy and an acceptable level of safety in the proposed indications.

The two test formulations of Levetiracetam Teva met the protocol-defined criteria for bioequivalence when compared with Keppra. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of both formulations was demonstrated.

## 2.4.7. Conclusions on clinical aspects

Based on the submitted bioequivalence studies, the following conclusions can be drawn:

The 1000 mg tablet under consideration is bioequivalent to the brand leader (Keppra 1000mg) after single dose under fasting conditions.

The 500 mg tablet under consideration is bioequivalent to the brand leader (Keppra 500mg) after single dose under fasting conditions.

The conclusions of these studies can be extrapolated to the lower strengths 750 mg and 250mg.

## *2.5. Pharmacovigilance*

### PSUR

The next data lock point for the reference medicinal product is 30 November 2011.

The PSUR of the reference medicinal product is on a yearly cycle. The PSUR submission schedule should follow the PSUR schedule for the reference product.

### Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk Management Plan

No Risk Management Plan was provided by the applicant since the application is based on a reference medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified. The applicant considers that levetiracetam is a well established active ingredient, which is been used for many years and the safety profile of the products is very well established.

Only routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation plan is not required.

The CHMP, having considered the above, was of the opinion that routine pharmacovigilance would be adequate to monitor the safety of the product.

## *2.6. User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

# 3. Benefit-Risk Balance

This application concerns a generic version of levetiracetam tablets. The reference product Keppra is indicated 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.

Keppra 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.

No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented. This was considered sufficient by the CHMP. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Two bioequivalence studies, both with a cross-over design under fasting conditions constitute the basis for this application. The study design was considered adequate to evaluate the bioequivalence of these formulations and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling times as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Levetiracetam Teva met the protocol-defined criteria for bioequivalence when compared with the Keppra. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

# 4. Recommendation

Based on the CHMP review of the available data the CHMP considers by consensus that the risk-benefit balance of Levetiracetam Teva 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; 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 and in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy, was favourable and therefore recommended the granting of the marketing authorisation.