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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Levetiracetam Actavis

International nonproprietary name: Levetiracetam

Procedure No. EMEA/H/C/002355

Note

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



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List of Abbreviations

alu – aluminium

ANOVA- Analysis of variance

ASMF – Active Substance Master File

AUC_{0-t} - area under the plasma concentration versus time curve from time zero to the last measurable concentration

AUC_{0-∞} - area under the plasma concentration versus time curve extrapolated to infinity

BE – Bioequivalence

BMI - Body Mass Index

CHMP - Committee for Medicinal Products for Human Use

CI- Confidence interval

C_{max} - Maximum measured plasma concentration

¹³C-NMR – Carbon-13 Nuclear Magnetic Resonance

EEA - European Economic Area

EMA – European Medicines Agency

EPAR – European Public Assessment Report

ERA - Environmental Risk Assessment

EU - European Union

EWP - Efficacy Working Party

FT-IR – Fourier Transform Infra-Red

GC – Gas Chromatography

GCP – Good Clinical Practice

GMP - Good Manufacturing Practice

¹H-NMR – Proton (also Hydrogen-1) Nuclear Magnetic Resonance

HDPE – High Density Polyethylene

HPLC – High Performance Liquid Chromatography

ICH – International Conference on Harmonisation

INN - International Nonproprietary Name

IPC - In-process Control

K_{el} - Elimination rate constant

LC-MS - Liquid Chromatography- Mass Spectroscopy

LDPE – Low Density Polyethylene

LOD - Limit of detection
LOQ - Limit of quantitation
MAH – Marketing Authorisation Holder
mg – milligram
ml - mililitre
MS – Mass Spectroscopy
N - number (of objects)
Ph Eur - European Pharmacopoeia
PK - Pharmacokinetics
pKa – Acid dissociation constant (also acidity constant)
PSUR – Periodic Safety Update Report
PVC - Polyvinyl chloride
QWP - Quality Working Party
q.s. - Quantum sufficit (as much as suffices)
RH – Relative Humidity
RMP – Risk Management Plan
SD - Standard deviation
SmPC – Summary of Product Characteristics
t_{1/2} - elimination or terminal half-life
T_{max} - time of maximum measured plasma concentration
T/R ratio – Test product /Reference product ratio
TSE/BSE *Transmissible spongiform encephalopathy /Bovine spongiform encephalopathy*
UV – Ultraviolet
XRD – X-ray diffraction

Background information on the procedure

1.1 Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 1 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam Actavis through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 March 2010.

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 Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

“Levetiracetam Actavis 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 Actavis 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 legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Kepra 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: Kepra 250, 500, 750, 1000 mg Film-coated tablets
 - Marketing authorisation holder: UCB Pharma S.A.
 - Date of authorisation: 29/09/2000
 - Marketing authorisation granted by: Community
 - Community Marketing authorisation number: EU/1/00/146/001-026, EU/1/00/146/029
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
 - Product name, strength, pharmaceutical form: Kepra 250, 500, 750, 1000 mg Film-coated tablets
 - Marketing authorisation holder: UCB Pharma S.A.
 - Date of authorisation: 29/09/2000
 - Marketing authorisation granted by: Community
 - Community Marketing authorisation number: EU/1/00/146/001-026, EU/1/00/146/029

- 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 1000 mg Film-coated tablets
 - Marketing authorisation holder: UCB Pharma S.A.
 - Date of authorisation: 29/09/2000
 - Marketing authorisation granted by: Community
 - (Community) Marketing authorisation number(s): EU/1/00/146/020-026
 - Bioavailability study protocol number: 842/06

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 Manufacturers

Manufacturer responsible for batch release

Actavis hf
Reykjavíkurvegur 76 - 78
IS-220 Hafnarfjörður
Iceland

1.3 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Alar Irs

- 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 17 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 March 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 April 2011.
- During the CHMP meeting on 16- 19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 June 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 July 2011.
- During the meeting on 18-21 July 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 Actavis on 21 July 2011.

2 Scientific discussion

2.1 Introduction

Levetiracetam Actavis is a generic medicinal product containing levetiracetam as active substance. Four strengths have been developed; 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets. The reference medicinal product Keppra has been centrally authorized on 29 September 2000 and exists as film-coated tablets of 250 mg, 500 mg, 750 mg and 1000 mg and as oral solution (100 mg/ml) and as concentrate for solution for infusion (100 mg/ml).

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 exact mechanism by which levetiracetam acts to treat epilepsy is unknown, however, the drug binds to a synaptic vesicle protein, SV2A which is believed to impede nerve conduction across synapses. 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.

According to the legislation the applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic of a reference product, which is authorised for 6/10 years in a EU member state or in the Community. Bioequivalence to the reference product Keppra was demonstrated by one bioequivalence study at single dose under fasting conditions. The studies were performed in healthy volunteers. One study was performed with the 1000 mg tablets.

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

The therapeutic indication of Levetiracetam Actavis is:

Levetiracetam Actavis 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 Actavis 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.

Levetiracetam Actavis is presented in packs of 20, 30, 50, 60, 100, 120 and 200 film-coated tablets for each strength; 250 mg, 500 mg, 750 mg and 1000 mg and in bottles of 30, 100 and 200 film-coated tablets for each strength. The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2 Quality aspects

2.2.1 Introduction

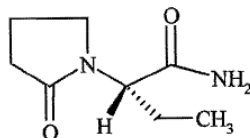
The drug substance is levetiracetam a pyrrolidone derivative, an analog of piracetam and belongs to a class of antiepileptics.

The product is supplied as a as film-coated tablets containing 250 mg; 500 mg 750 mg and 1000 mg levetiracetam. The product will be marketed in Al/Al blisters or HDPE containers with LDPE lid.

For a full list of excipients refer to the SmPC.

2.2.2 Active Substance

The INN name of the active substance is levetiracetam and the chemical name (S)-2-(2-oxopyrrolidin-1-yl)butanamide. The molecular formula of active substance is $C_8H_{14}N_2O_2$ its relative molecular mass 170.2 and its structural formula is shown below.



Levetiracetam appears as a white to off-white non-hygroscopic powder, very soluble in water and soluble in methanol and in acetone. The pKa of levetiracetam is < -2 and can not be determined with accuracy due to the chemical instability of the protonated form.

It has an asymmetric centre with S-configuration and it is controlled by the test for specific optical rotation. The R-isomer is controlled by HPLC test.

Levetiracetam produced by the proposed active substance supplier is of crystalline form. The consistency of the form has been established by XRD on three consecutive batches.

Manufacture

The active substance is supported by an ASMF. The manufacturing process has been described in sufficient detail and yields the desired crystal form. If required, reprocessing of any intermediate or drug substance batch is foreseen in accordance with ICH Q7A guideline by repeating all or part of the related process step.

Sufficient information has been presented regarding the critical steps and intermediates, including in-process controls (IPC).

Sufficient information regarding the carry over of related substances including the impurities with potential genotoxic alert has been presented and suitable specifications are proposed.

Specification

Levetiracetam is described in the last edition of the European Pharmacopoeia (Ph. Eur.). The Ph. Eur. monograph specifications have been implemented by the finished product manufacturer, where applicable, to control of the active substance. The specification includes tests and limits for appearance (visual), solubility (Ph.Eur.), appearance of solution (Ph.Eur.), identification (IR), enantiomeric purity (Ph.Eur.), specific optical rotation (Ph. Eur.), assay (HPLC), related substances (HPLC), sulphated ash (Ph.Eur.), heavy metals (Ph. Eur.), water content (Ph. Eur.), residual solvents (GC) and particle size (laser diffraction).

In-house analytical procedures have been described and validated. Impurities have been evaluated and found to be acceptable from the safety viewpoint.

The certificates of analysis of three consecutive commercial scale batches manufactured by the active substance manufacturer were enclosed to the Open Part of ASMF. The batch analysis results obtained according to the updated proposed specifications will also be provided by the applicant when available.

Stability

Stability studies were performed on three commercial scale batches for up to 24 months at long-term conditions (25°C/60%RH) and for six months in accelerated conditions (40°C/75%RH). Supportive data for another three smaller scale batches stored for 60 months at long-term conditions and for six months in accelerated conditions have also been presented. The data submitted support the proposed re-test period.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

Levetiracetam is an antiepileptic drug available marketed as 250 mg, 500 mg, 750 mg and 1000 mg tablets.

The aim of the formulation study was to develop immediate-release product lighter and smaller, but with similar quality as the reference product on the market Keppra. All the strengths are dose proportional.

The particle size of the active was found to have a considerable influence on disintegration and dissolution. The finer particle size gives faster disintegration/dissolution at all time points compared to the coarser material.

The formulation was modified to ensure better manufacturability to improve dissolution rate and to improve pharmacotechnical characteristics. The wetting was adjusted, a different grade of disintegrant was used, the amount of lubricant was optimised. These changes improved the disintegration time significantly.

Active substance from two sources has been used initially and based on stability results and technical properties the most favourable material and supplier was selected.

The excipients used in the tablet formulation as proposed for marketing are well known and widely used in the pharmaceutical industry and except for tablet coating agent Opadry II, all other substances are described in the European Pharmacopoeia. No incompatibilities between them and the drug substance are known.

In-vitro dissolution profiles of the biobatches at three different pH values and in water were presented. The results revealed that there is no critical difference between the dissolution of the test and reference products at all 3 buffers tested as levetiracetam is very soluble at these pH values.

The manufacturing method is a standard wet granulation method.

The proposed packaging materials are Al/PVC blisters and HDPE container with LDPE cap.

Adventitious agents

There are no excipients of human or animal origin in Levetiracetam Actavis tablets.

Manufacture of the product

The method of manufacture is wet granulation, followed by drying and mixing and tablet compression. The final step is coating of the tablets. The manufacturing process has been described in sufficient detail.

The process validation schemes of the drug products were presented and the manufacturing process will be validated according to the process validation protocol on first three consecutive production batches of each strength.

Product Specification

Adequate release and shelf-life specification have been presented for the finished product and include tests and limits for: appearance (visual examination), identification (levetiracetam HPLC, UV), dissolution (Ph. Eur.), Disintegration (Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), microbial test (Ph. Eur.), resistance to crushing (Ph. Eur.), average weight (Ph. Eur.) and identification of colorants.

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

The formal stability program consists of two pilot scale batches of each strength, packed in the two proposed packaging materials. Thirty-six months results at $25\pm 2^{\circ}\text{C}/60\pm 5\%$ RH, twelve months results at $30\pm 2^{\circ}\text{C}/65\pm 5\%$ RH and six months results at $40\pm 2^{\circ}\text{C}/75\pm 5\%$ RH are available for the pilot scale batches manufactured with drug substance from the proposed active substance supplier and packed in the two proposed packaging materials.

Stability in bulk

A bulk stability study was conducted for 6 months. The formal stability program consists of one pilot scale batches of each strength. The purpose was to monitor the stability of the product in bulk container (plastic bags inside a 15 L bulk container for 15 L container for 6 months, tested at 0, 3 and 6 months time points. The same analytical methods were used in the stability program as for release. The shelf-life specification was followed in this study.

Stability of the open bottle packaging

Tablets were stored in HDPE bottle for 6 months at $25^{\circ}\text{C}/60\%$ RH, tested up to 6 months. The same analytical methods were used in the stability program as for release. The shelf-life specification was followed in this study. No significant changes or out of specifications results were observed.

Photostability studies

In order to assess the stability of Levetiracetam Actavis tablets against degradation by light a photostability test according to the current ICH Q1B Guideline on *Photostability Testing of New Active Substances and Medicinal Products* has been carried on. Provided data have been found sufficient.

Based on the overall data it can be concluded that the proposed shelf life and storage conditions of the finished product in the packaging described can be accepted.

2.2.4 Discussion on chemical, and pharmaceutical 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.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6 Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Drug substance

The batch analysis results obtained according to the updated specifications should be provided when available.

Drug product

Process validation report for commercial batches of the finished product will be finalised by the end of August 2011 and the report should be submitted as soon as available.

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 Actavis 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 ERA 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 film-coated tablets containing Levetiracetam. To support the marketing authorisation application the applicant conducted 1 bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study 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 trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

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 one bioequivalence study with Levetiracetam Actavis 1000 mg film-coated tablets.

This approach is considered acceptable as all the conditions set forth in section 4.1.6. of the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1* are fulfilled:

- a) The Levetiracetam Actavis 250, 500, 750, 1000 mg film-coated tablets are manufactured by the same manufacturing site and manufacturing process;
- b) The qualitative composition for all four strengths is the same;
- c) The formulation for of all four strengths is dose-proportional (Table 1);
- d) The dissolution profiles of different strengths are similar over the physiological pH range;
- e) Levetiracetam has shown to display linear pharmacokinetics over the therapeutic range.

Table 1. Composition of the Levetiracetam Actavis tablets

	250mg tablets	500mg tablets	750mg tablets	1000mg tablets
<i>Active ingredient</i>				
Levetiracetam	250 mg	500 mg	750 mg	1000 mg
<i>Excipients</i>				
Crospovidone	8.25 mg	16.50 mg	24.75 mg	33.0 mg
Povidone	7 mg	14 mg	21 mg	28 mg
Silica colloidal anhydrous	3.50 mg	7.0 mg	10.5 mg	14 mg
Magnesium stearate	1.25 mg	2.50 mg	3.75 mg	5.00 mg
Water purified*	q.s.	q.s.	q.s.	q.s.
<i>Total weight of tablet core:</i>	270 mg	540 mg	810 mg	1080 mg

* Not present in the final formulation

2.4.2 Pharmacokinetics

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study:

- Study no. 842/06 is a single dose (under fasting conditions) trial. This study has investigated the 1000 mg strength.

Methods

Study design

The study was an open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 8 days between two administrations. One tablet containing 1000mg of Levetiracetam was administered in each period.

CRO and principal investigator: Lotus Labs Pvt. Ltd., #56 Ragas Building, Dr. Radhakrishnan Salai, Opp. CSI Kalyani Hospital, Mylapore, Chennai- 600 004, India. The principal investigator was Dr. S.Kala.

Site and dates of clinical part of the study: Lotus Labs Pvt. Ltd., #56 Ragas Building, Dr. Radhakrishnan Salai, Opp. CSI Kalyani Hospital, Mylapore, Chennai- 600 004, India; 19/07/2006 to 08/09/2006

Site and dates of analytical part of the study: Lotus Labs Pvt. Ltd., No.7, Jasma Bhavan Road, Millers Tank Bed Area, Opp. Gurunanak Bhavan, Vasanthanagar, Bangalore-560 052, India; 06/09/2006 to 14/09/2006

Protocol number: No 842/06 version 3.0 dated 16/06/2006. The Ethics Committee has approved study protocol on 13/07/2006. Study was initiated after obtaining approval from the Indian Regulatory Authority- Drug Controller General of India.

The final report is dated 17/11/2006.

Biostatistician and biostatistical institute: Mr. Mani Kandasamy, Lotus Labs Pvt. Ltd.

Food and fluid intake: Subjects were housed in the clinical facility at least 13 hours before drug administration until 24 hours after drug administration. Study drug was taken after an overnight fast with 240ml water. The first meal was served 4 hours after drug administration; following meals were served at appropriate time thereafter. Water was not permitted 1 hour before until 2 hours after drug administration.

Sampling schedule: 19 blood samples were collected for the assessment of Levetiracetam concentrations as follows: 1 hour before dosing (0, pre-dose) and at 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.0, 1.33, 1.67, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0 and 36 hours after administration of study drug.

The study was conducted in accordance with the Declaration of Helsinki and GCP. Study sites have been recently inspected for GCP/GLP compliance by several international authorities.

The CHMP considers the study design appropriate and in line with pharmacokinetic properties of Levetiracetam; the sampling time schedule and wash-out period is adequate taking into account the elimination half-life of the drug.

Test and reference products

Levetiracetam Actavis 1000 mg film-coated tablets manufactured by Actavis Group PTC ehf (batch No. 94445, batch size: 100 000 tablets, manufacturing date 13/02/2006; retest date: 08/2006) has been compared to Keppra 1000 mg film-coated tablets marketed by UCB Pharma S.A., Belgium (Batch No: 0000015921, exp. date 11/2008).

The CHMP considers that Keppra 1000 mg film-coated tablets, the reference product, is the appropriate choice, since it is a well-known medicinal product authorised within EU community.

Population(s) studied

28 healthy Indian (South Asian) male volunteers (age 18-35 years) were planned and enrolled in the study. 27 volunteers completed both study phases and were included in the pharmacokinetic and statistical analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a bioequivalence study and for the product under investigation.

Drop outs: Subject No.24 did not check in for Period II.

The CHMP considers that the population was chosen according to the scientific guidelines and the sample size is found adequate.

Analytical methods

Plasma concentrations of Levetiracetam were determined using a validated LC-MS/MS method. Study drug was isolated from plasma by solid phase extraction. Imipramine was used as the internal standard.

The calibration curve ranged from 0.7059 to 101.2009 $\mu\text{g/ml}$ and the LLQ was 0.7049 $\mu\text{g/ml}$ for Levetiracetam in plasma.

The quality control samples contained 0.7270, 1.9808, 33.6871 and 76.5615 $\mu\text{g/ml}$ of Levetiracetam in plasma.

The plasma samples were stored at -20°C until analysis in 24 analytical sequences. Within study validation was shown based on back-calculated concentrations of quality control (QC) samples. Long term stability of Levetiracetam in plasma was shown at -20°C for 85 days covering the real storage time of study samples (i.e. 57 days). Analytes stability at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation.

76 (~7.3%) out of the 1045 samples in the study were reanalyzed because 2 analytical sequences (Subjects No.3 and No.11) for Levetiracetam did not meet the SOP acceptance criteria.

All concentration values below limit of quantification were set as zero for PK analysis.

The CHMP considers that the analytical part of the study was performed in accordance with GLP principles. The handling of samples has been described in a comprehensive manner and the relevant SOPs were provided.

The analytical method had been sufficiently validated (pre-study and within study) in order to determine the plasma levels of Levetiracetam.

Pharmacokinetic Variables and Statistical methods

Pharmacokinetic parameters C_{max} , AUC_{0-t} , $\text{AUC}_{0-\infty}$, $\text{AUC}_{0-t}/\text{AUC}_{0-\infty}$, T_{max} , $T_{1/2}$ and K_{el} were determined.

Primary variables were considered AUC_{0-t} , $\text{AUC}_{0-\infty}$ and C_{max} .

AUC_{0-t} was calculated using the linear trapezoidal rule. Non-parametric analysis of T_{max} on untransformed data was performed using the methods of Koch. PK parameters for each individual were tabulated and graphically presented. Pharmacokinetic parameters were calculated using the WinNonlin 4.1. The mean percentage of extrapolated area under the curve was lower than 20% for both test and reference product and for all study subjects. None of the pre-dose samples contained detectable levels of Levetiracetam.

Statistical analysis of the log-transformed data was performed on SAS 9.1 software using GLM procedure. ANOVA model included sequence, period and treatment as fixed effects and subjects nested within sequence as random effect. Ratio of the means and 90% CI of the ratio for C_{max} , AUC_{0-t} and $\text{AUC}_{0-\infty}$ were calculated by taking the anti-log value of the difference of least square means from ANOVA.

Criteria for conclusion of bioequivalence:

For both, AUC_{0-t} and C_{max} , the 90% confidence interval for the ratio of test/reference for the population means derived from logarithmically transformed data should lie within the conventional 80-125% limits.

The CHMP considers that the pharmacokinetic parameters calculated are justified and statistical methods appropriate for a single dose study. Standard bioequivalence criteria are proposed for AUC_{0-t} and C_{max} .

Results

Levetiracetam pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Treatment	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}	$T_{1/2}$
	$\mu\text{g/ml/h}$	$\mu\text{g/ml/h}$	$\mu\text{g/ml}$	h	h
Test (SD)	301.2928 (47.1908)	314.8851 (47.4805)	30.2152 (5.8689)	0.95	7.29
Reference (SD)	306.3845 (48.1311)	318.3803 (48.0835)	31.8426 (13.3503)	1.16	7.23
*Ratio (90% CI)	0.98	0.99	0.99		
CV (%)	4.72	4.52	17.33		
$AUC_{0-\infty}$ 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					

*In-transformed values

Safety data

Neither serious adverse events nor adverse events were reported during the study. All the laboratory values were within clinically acceptable range. Both products, the test and the reference, were found to be well tolerated.

Conclusions

Based on the presented bioequivalence study Levetiracetam Actavis 1000mg film-coated tablet is considered bioequivalent with Keppra1000mg film-coated tablet.

The results of study 842/06 with 1000 mg formulation can be extrapolated to the lower strengths 750 mg, 500 mg and 250 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6

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

The results of one bioequivalence study have been presented. The study was an open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 8 days between two administrations. One tablet containing 1000 mg of Levetiracetam was administered in each period.

The 90% confidence intervals for the test and reference mean ratio of the log-transformed pharmacokinetic variables C_{max} , $AUC_{0-\infty}$ and AUC_{0-t_r} were within the conventional bioequivalence range of 80% to 125%.

Based on the submitted bioequivalence study Levetiracetam Actavis 1000mg film-coated tablets by Actavis Group PTC ehf., Iceland is considered bioequivalent with the reference product Keppra 1000mg film-coated tablets by UCB Pharma S.A., Belgium.

2.4.7 Conclusions on clinical aspects

Based on the presented bioequivalence study Levetiracetam Actavis 1000mg film-coated tablet is considered bioequivalent with Keppra 1000mg film-coated tablet.

The results of study 842/06 with 1000 mg formulation CAN be extrapolated to the lower strengths 750 mg, 500 mg and 250 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The CHMP did not require the applicant to submit a risk management plan because 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 CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR cycle

The PSUR submission schedule should follow the PSUR submission schedule for the reference medicinal 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 film coated tablets. The reference product Keppra 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 and considered sufficient. 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.

One bioequivalence study under fasting conditions constitutes the basis for this application. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time 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 Actavis 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 data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Levetiracetam Actavis 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 Actavis 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",

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management System

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.