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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Levetiracetam Accord

International non proprietary name: levetiracetam

Procedure No. EMEA/H/C/002290

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of Abbreviations

Alu	Aluminium
ANOVA	Analysis of variance
ASMF	Active substance master file
AUC_{0-t}	Areas under the concentration-time curve from 0 to last measurable concentration and
AUC0-inf	Area extrapolated to infinity
BE	Bio-equivalence
BMI	Body Mass Index
CHMP	Committee for Human Medicinal products
CI	Confidence interval
C_{max}	Peak plasma concentration
ECG	Electrocardiogram
EEA	European Economic Area
EMA or EMEA	European Medicines Agency
EPAR	European Public Assessment report
ERA	Environmental Risk Assessment
EU	European Union
EWP	Efficacy Working Party
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
INN	International Nonproprietary Name
IR	Infrared
LLOQ	Lower limit of quantification
MS	Mass spectrometry
N	Number (of objects)

NRG	Name Review group
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PVC	Polyvinyl chloride
QWP	Quality Working Party
RH	Relative humidity
SD	Standard deviation
SmPC	Summary of Product Characteristics
T/R ratio	Test to Reference ratio
$T_{1/2}$	Half-life
TSE/BSE	Transmissible spongiform encephalopathy/Bovine spongiform encephalopathy
T_{max}	Time to Cmax
ULOQ	Upper limit of quantification
UV	Ultra-violet
UV-VIS	Ultra-violet and visual light
XRD	X-ray diffraction

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Accord Healthcare Limited submitted on 4 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised medicinal product'.. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP during its meeting on 15 – 18 February 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 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 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 Keppra instead of non-clinical and clinical unless justified otherwise.

■ 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 number: EU/1/00/146/001-026 and EU/1/00/146/028-029

■ 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
- Marketing authorisation number: EU/1/00/146/001-026 and EU/1/00/146/028-029

■ 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 SA
- Date of authorisation: 29-09-2000
- Marketing authorisation granted by: Community
- Marketing authorisation number: EU/1/00/146/022
- Bioavailability study number: 094-07

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 Rapporteur appointed by the CHMP was:

Rapporteur: Pieter Neels

- The application was received by the EMA on 4 October 2010.
- The procedure started on 17 November 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 February 2011.
- During the meeting on 14 to 17 March 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 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 July 2011.
- During the meeting on 18 to 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 Accord on 21 July 2011.

2 Scientific discussion

2.1 Introduction

Levetiracetam Accord 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 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.

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 a one single dose bioequivalence study under fasting conditions for the 1000 mg tablet. The study was performed in healthy volunteers.
The indication proposed for Levetiracetam Accord is identical to the indication of the reference medicinal product.

The therapeutic indication of Levetiracetam Accord is:

Levetiracetam 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 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 Accord is presented in seven pack sizes; 10, 20, 30, 50, 60, 100, and 200 film-coated tablets for each strength; 250 mg, 500 mg, 750 mg and 1000 mg. At the time of the CHMP opinion, the 10 tablets pack size does not exist for the 250 mg and 750 mg strength of the reference product. Nevertheless, the proposed pack sizes are consistent with the dosage regimen and duration of use.

The applicant applied for a combined printed package leaflet. During its plenary meeting in November 2010, the Name Review group (NRG) agreed to that request.

2.2 Quality aspects

2.2.1 Introduction

Levetiracetam Accord is presented as film-coated tablets containing the active substance levetiracetam. Four strengths have been developed: 250 mg, 500 mg, 750 mg and 1000 mg. Other ingredients are defined in the SmPC, section 6.1. The different strengths can be distinguished by the tablet colour and debossing. The tablets are packed in PVC-aluminium blisters.

Levetiracetam is an established active substance of chemical origin and is described in the European Pharmacopoeia. The ASMF procedure is used and declarations from the Qualified Person have been provided to confirm the active substance is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

2.2.2 Active Substance

This medicinal product contains as active substance levetiracetam INN, chemical name (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide. The molecular formula is $C_8H_{14}N_2O_2$ Mol.Wt. 170.21 g/mol. Levetiracetam appears as a white or almost white powder and is very soluble in water, soluble in acetonitrile and practically insoluble in hexane.

Levetiracetam is not hygroscopic. It exhibits isomerism due to the presence of one chiral center, and does not present polymorphism.

Manufacture

At the time of the CHMP opinion, the active substance used for Levetiracetam Accord is supplied by one active substance manufacturer. Because no Ph.Eur. certificate of suitability has been issued for the active substance manufactured by the proposed supplier, detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of an active substance master file (ASMF). The manufacturing process is adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized. The applicant confirmed the structure of the levetiracetam by ^{1}H NMR, ^{13}C NMR and MS. The molecular weight was determined by elemental analysis. The consistency of crystalline form of levetiracetam is checked by XRD analysis. Statements from the Qualified Persons of the finished product manufacturers confirming that the manufacturing of the active substance is performed in compliance with current EU GMP or ICH Q7A were provided.

Specification

There is a Ph.Eur. monograph for levetiracetam and hence the active substance is tested according to the Ph.Eur monograph, complemented with in-house tests and specifications defined by the applicant. The active substance specifications include tests as: appearance, solubility, identification (IR, optical rotation, enantiomeric purity), appearance of solution, water, sulphated ash, heavy metals, enantiomeric purity (HPLC), related substances and assay (HPLC), residual solvents, triethylamine and particle size.

The specifications and tests proposed by the applicant are compliant with the relevant ICH guidelines and Ph.Eur. In-house methods have been adequately validated. The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data (certificates of analysis) have been provided on at least two production batches of levetiracetam manufactured by the proposed supplier. All batches were in compliance with the

predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

The active substance levetiracetam is packaged in packaging materials that comply with Directive 2002/72/EC and Ph.Eur. and is safe for use in contact with food stuffs and pharmaceuticals. The container closure system is described in sufficient detail and the packaging materials are acceptable.

Stability studies on the active substance have been performed at long term (30±2°C/65±5% RH) and accelerated (40±2°C/75±5% RH) conditions on three production scale batches as per ICH Guidelines. Up to 3 years of long term stability data, and up to 6 months of accelerated stability data has been provided, confirming the stability of the active substance. Up to 5 years long term stability data is available for several smaller batches. All batches have been tested for conformance with the specifications using stability indicating analytical methods. In all cases the batch analysis data met the predefined specifications and no significant trends were observed. The packaging used in stability trials is representative for the one proposed for storage and distribution. Every year one production batch will be put under long-term stability program.

Forced degradation studies have been performed. Samples were exposed to NaOH, HCl and H_2O_2 light. From this study, it can be concluded that degradation takes place, leading to an increased amount of impurities. However, no degradation was observed during photolytic treatment (24 hours exposure to direct sun light).

The stability data provided support the proposed retest period in the proposed packaging and under the proposed storage conditions.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The applicant's objective was to develop a generic equivalent to the European reference product Keppra film-coated tablets containing 250 mg, 500 mg, 750 mg and 1000 mg levetiracetam. The aim was to develop generic film-coated tablets which are bioequivalent with the reference product and demonstrate to be robust and stable, having a dissolution profile matching with the reference product.

Levetiracetam Accord film-coated tablets contain partially the same excipients as the reference medicinal product Keppra. A compatibility study demonstrated that the chosen excipients are compatible with the active substance. The core of the Keppra tablet is made of croscarmellose sodium, macrogol 6000, silica colloidal anhydrous and magnesium stearate. The core of the Levetiracetam Accord tablet contains povidone K-30 instead of macrogol 6000. Like the reference product, the Levetiracetam Accord tablets are film-coated, but the composition of the coating is not always exactly the same as for Keppra. All excipients used in the tablet core comply with the Ph.Eur. and are commonly used in this type of formulation. The excipients used in the film-coating, and which are not Ph.Eur grade, are of adequate quality. The generic formulation is not considered to be significantly different from the originator's formulation.

During the development, the applicant investigated the reference product Keppra for chemical characteristics i.e. assay, related substances and dissolution profile. The product development work was initiated with the 1000 mg strength and the lower strengths were developed to be dose proportional. The development aimed at achieving satisfactory physical tablet parameters like hardness, friability and disintegration time after film-coating.

Comparative multimedia dissolution profiles between test and reference product are presented for the 4 strengths: the dissolution profiles of the test and reference product are comparable in all tested media (purified water, 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). It can be concluded that the Levetiracetam Accord and Keppra film-coated tablets have equivalent release of the active substance.

Levetiracetam Accord film-coated tablets were developed in four different strengths, i.e. 250 mg, 500 mg, 750 mg and 1000 mg. The bioequivalence study was performed with the 1000 mg tablet. The

applicant fulfilled the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) and extrapolated the results of the bioequivalence study performed on the 1000 mg strength to three lower strengths; 250 mg, 500 mg and 1000 mg. Appropriate *in vitro* dissolution data confirmed the adequacy of waiving additional *in vivo* bioequivalence testing.

Adventitious agents

A TSE declaration was submitted to confirm that magnesium stearate is of vegetable origin. The excipients used do not contain and are not derived from any category A or B as defined in the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2). The TSE/BSE free certification from the supplier of drug substances and all the excipients is provided.

Manufacture of the product

The manufacturing process is a standard process for film-coated tablets. All critical process parameters have been identified and controlled by appropriate in process controls. The test methods and acceptance criteria are adequately chosen to ensure that the drug product will comply with the specification limits. A detailed manufacturing description and flow scheme have been provided.

Process validation has been carried out on three consecutive commercial scale batches of each strength. The results obtained indicate that the manufacturing process for the levetiracetam film-coated tablets is capable of consistently producing tablets that meet the quality and release specifications as detailed in the finished product specifications

Product Specification

The finished product release specifications include tests for description, average tablet weight, identification (HPLC, IR, TiO_2), uniformity of dosage units, dissolution (HPLC), assay, related substances and degradation products (HPLC), microbiological tests and subdivision of tablets. The finished product specifications are standard for film-coated tablets. The proposed test procedures and acceptance criteria comply with the ICH guidelines and the general requirements of the Ph.Eur. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.
Batch analysis data (certificates of analysis) are provided for three commercial scale batches of each strength, produced with active substance from the proposed supplier. The batches were manufactured according to the proposed manufacturing process and packed in the packaging material as proposed for the market. Batch analysis results comply with the predefined specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies have been carried out under long term (25±2°C/60±5%RH) and accelerated (40±2°C/75±5% RH) conditions, on three commercial scale batches of each strength according to the ICH requirements. Up to 36 months long term and up to 6 months accelerated stability data have been provided.

The stability samples have been tested for description, related substances, assay, dissolution, microbial contamination and breakability. The specifications and test methods used were identical to those for batch release. The methods used for assay and related substances were proven as stability indicating. The stability batches have been manufactured at the proposed site of finished product manufacture, according to the proposed process and using the active substance obtained from the proposed active substance manufacturer. Stability tests have been carried out in the packaging proposed for marketing. During accelerated and long term stability studies, all the tested parameters were within shelf life acceptance criteria and no significant trend was observed.

In addition to the above, a long term bulk stability study was performed on two commercial scale batches for each strength. The same parameters as above were tested and all were within shelf life acceptance criteria and no significant trend was observed.

Furthermore, a forced degradation study was carried out by water, acid and base hydrolysis, by oxidative degradation, thermal degradation and UV light degradation to proof the stability indicating capacity of the test methods.

Finally, a photostability study was carried out as per ICH guidelines on a 1000 mg tablet batch. The tablets were either packed in PVC/Alu blister (immediate pack) or in PVC/Alu blister into carton (marketing pack). The samples were tested after total exposure to UV and visible light and the results indicate that the product is photostable in the proposed pack.

As part of the stability commitment, the applicant committed that at least one batch of Levetiracetam Accord film-coated tablets will be placed on stability annually.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Levetiracetam Accord 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets is a generic product for Keppra film-coated tablets, containing very similar excipients to Keppra.

The quality of the active substance is adequately controlled and all excipients comply with the Ph.Eur. or meet adequate specifications. The finished product manufacturing process shows to be capable of consistently producing tablets that meet the finished product specifications and appropriate packaging is used to ensure the product remains stable within the agreed shelf-life.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and medicinal product has 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.

The quality of this medicinal product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

2.2.6 Recommendations for future quality development

Not applicable.

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.

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 Accord 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 this justification.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for film-coated tablets containing levetiracetam. To support the marketing authorisation application the applicant conducted one single dose bioequivalence study under fasting conditions with the 1000 mg dosage strength. 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 film-coated tablets 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 the clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Lambda Therapeutic Research Ltd. has been inspected by WHO and national authorities over the period between 2004 and 2009 and was found compliant with ICH GCP requirements.

Exemption

Four different strengths of levetiracetam tablets (250, 500, 750 and 1000 mg) have been developed. All four strengths are scale-up/scale down formulations with ratio of active substance to excipients remaining the same for all strengths.

The application of the four dosage strengths is based on the bioequivalence study with Levetiracetam 1000 mg film-coated tablets, Accord Healthcare Ltd.

This is considered acceptable, i.e. the bioequivalence can be established with only the 1000 mg dosage strength as all conditions specified in section 4.1.6 of the Note for guidance on the Investigation of Bioequivalence are fulfilled:

a) The products Levetiracetam Accord 250 mg, 500 mg, 750 mg & 1000 mg are manufactured by the same manufacturing process and manufacturing site;

b) The qualitative composition of all the four strengths is the same;

c) The formulation of all the four strengths is dose proportional;

d) In-vitro dissolution profiles are comparable between the strength used in BE study and additional strengths at the three pHs (1.0, 4.5 and 6.8). Release of more than 85% after 15 minutes;

e) Linear pharmacokinetics over the therapeutic range[1].

Clinical studies

To support the application, the applicant has submitted one single dose bioequivalence study under fasting conditions conducted in 2007 (study n°094-07).

2.4.2 Pharmacokinetics

Methods

Study design

The study was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, two-way cross-over, single oral dose, comparative oral BE study of Levetiracetam Accord 1000 mg film-coated tablets in comparison with Keppra 1000 mg film-coated tablets in healthy adult human subjects aged between 18-55 years under fasting conditions.

Subjects were administered a single dose of either the test or reference study medication, as a 1 x 1000 mg tablet with 240 ml of water. Single dose of either of the investigational medicinal products was administered orally to each subject (except for the discontinued subjects) in each period. A wash-out period of five days was maintained between the successive dosing days. Equal allocation of treatment sequence was carried out as per the randomisation schedule.

The sampling schedule was planned to provide a reliable estimate of the extent of absorption. 24 blood samples were collected from each subject during each period to analyze the pharmacokinetic profile of the test and of the reference drug.

A total of 1355 blood samples were collected during the study. 23 blood samples from each subject were collected during each period. The samples were collected prior to drug administration and at 0.25, 0.50, 0.75, 1.00, 1,25 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours following the drug administration in each period.

Test and reference products

Levetiracetam Accord 1 x 1000 mg tablet manufactured by Intas Pharma Ltd., Matoda, India (Batch n°H2694, expiry date: March 2009, batch size: 110 000 tablets) was compared to Keppra 1 x 1000 mg tablet manufactured by UCB Pharma S.A., Belgium (Batch n°29258/1, expiry date: October 2009). Keppra 1000 mg tablets are registered via centralised procedure (EU/1/00/146).

The Certificates of analysis (test and reference products) complied with the acceptance specifications. The assayed content of the batch used as test product did not differ more than 5 % from that of the batch used as reference product (101.9% and 99.7% for Levetiracetam Accord and Keppra, respectively).

[1] Patsalos Philip N. Clinical Pharmacokinetics of Levetiracetam. Clin Pharmacokinet 2004; 43 (11): 707-724.

Population studied

The sample size was determined based on an intra-subject variability of approximately 16% (based on in-house estimates), a T/R ratio of 90-110%, a significance level of 5%, a power of > 80% and bioequivalence limits of 80-125%. Based on the above estimates, a sample size of 30 subjects was considered to be sufficient to establish bioequivalence with adequate power.

Healthy male volunteers, aged between 18-55 years, with BMI between 18.5-24.9 kg/m^2, having no significant diseases or clinically significant abnormal laboratory values during screening, medical history, clinical examination, chest X-ray or ECG were enrolled in the study. A total of 32 subjects including two additional subjects were checked in for the trial. Two additional subjects were checked in for the trial in order to account for any dropouts prior to dosing in period I. As per the protocol, 30 subjects were dosed in period I of the trial. One subject discontinued from the trial on his own accord prior to dosing in period I and was replaced by one of the two additional subjects. Two other subjects discontinued from the trial on their own accord. 27 subjects completed the clinical phase of the trial successfully. The plasma samples of these 27 subjects who completed the clinical phase of the trial and the plasma samples of one subject, who was withdrawn from the trial on medical grounds, were analysed as per the requirement of the protocol.

Analytical methods

The plasma concentrations of levetiracetam in the study samples were quantified by a validated HPLC method. Concerning validation of the bioanalytical method, information on linearity, accuracy and precision, recovery, robustness, selectivity, dilution integrity, matrix effect, short and long term stability was provided in the dossier. The CHMP considered that these characteristics were described correctly and within the acceptance specifications as applicable. The analytical method used was shown to be sensitive, accurate and selective for the plasma level determination of levetiracetam in the concentration range of 1.006-40.001 µg/ml. The lower limit of quantification (LLOQ) was 1.006 µg/ml of plasma. Concentrations below the lower limit of quantification were considered non-quantifiable.

The validation report provided results of short- and long-term (storing for 489 days in the freezer maintained at -22 ± 5°C and at -65± 5°C) stability data. The study sample storage period from collection until the completion of analysis was 26 days). Considering the long-term stability data, the maximal sample storage period was covered.

Dilution integrity for levetiracetam was evaluated by preparing samples with 3-4 times the concentrations of the highest standard. A sample of levetiracetam having concentration of 128.035 µg/ml was prepared in plasma and this was diluted to 1/5 and 1/10 of the original concentration. The percent accuracy of the dilution integrity samples was within the acceptance criteria of 85-115% of nominal. The CHMP considered that dilution integrity was correctly evaluated with an analyte concentration well above the upper limit of quantification (ULOQ).

The chromatographic system was tested in order to evaluate the possibility of carry-over. The carry-over experiment was performed and no carry-over was observed at the retention time and transition of levetiracetam and zonisamide.

A total of 1312 samples were analyzed during the study. A total of 20 re-analyses of individual analyses were carried out in duplicate in the study for the following reasons: 13 samples were reanalyzed due to concentrations above the highest standard, six samples were reanalyzed due to elimination of low calibration curve standard and one sample was reanalyzed due to significant variation in response of the internal standard. The criteria for rejection of individual samples for

analytical reasons were considered acceptable, in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1.)

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.

The following standard PK parameters were calculated: peak plasma concentration (C_{max}), time to C_{max} (T_{max}), areas under the concentration-time curve from 0 to last measurable concentration (AUC_{0-t}) and area extrapolated to infinity (AUC_{0-inf}).

Statistical methods

Descriptive statistics was computed and reported for all pharmacokinetic parameters of levetiracetam.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for un-transformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were computed for Levetiracetam using PROC MIXED of SAS Release 9.1.3. (SAS Institute Inc., USA).

ANOVA model included sequence, formulation and period as fixed effects and subject (sequence) as a random effect. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

Formulation, period, and sequence effects for ln-transformed data were found to be statistically insignificant.

The 90% parametric confidence intervals were calculated for the un-transformed and ln-transformed pharmacokinetic parameters, C_{max}, AUC_{0-t} and AUC_{0-inf} of levetiracetam.

Intra-subject variability and power were calculated for un-transformed and ln-transformed PK parameters.

Bioequivalence of Test Product-B vs. Reference Product-A was concluded, if the 90% confidence interval fell within the acceptance range of 80-125% for ln-transformed pharmacokinetic parameters Cmax and AUC_{0-t} for levetiracetam.

Results

The results of the study are presented in table below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, ratio (90% CI)) N=27

Treatment	**AUC_{0-t}** **xg/ml/h**	**$AUC_{0-\infty}$** **xg/ml/h**	**C_{max}** **xg/ml**	**t_{max}** **h****	**$T_{1/2}$** **h**
Test	320.92 ± 53.09	342.21 ± 49.40	33.48 ± 6.42	0.75 (0.5-2.5)	7.41 ± 0.88
Reference	328.59 ± 57.02	346.57 ± 56.32	36.92 ± 7.89	0.5 (0.5-2.0)	7.55 ± 0.89

Ratio (90%CI)*	98 (95–101)	99 (97–101)	91 (84–99)	-	-
CV (%)	6.4	5.1	17.8	-	-

$AUC_{0-\infty}$ **area under the plasma concentration-time curve from time zero to infinity**
AUC_{0-t} **area under the plasma concentration-time curve from time zero to t hours**
C_{max} **maximum plasma concentration**
T_{max} **time for maximum concentration**
$T_{1/2}$ **half-life**

*ln-transformed values, ** Median (min,max) values for Tmax

The 90% confidence intervals around the geometric means ratio T/R for levetiracetam were in the acceptance range of 80-125% for the primary parameters AUC0-t, AUC0-inf and Cmax.

Therefore, the bioequivalence under fasting conditions between Levetiracetam Accord 1000 mg tablets and Keppra 1000 mg tablets can be considered as demonstrated.

Safety data

All subjects except for those who discontinued were exposed to 1000 mg of levetiracetam once in each period as per the randomisation schedule with a wash-out period of five days between the successive dosing days. A total of nine adverse events were reported during the conduct of the trial. One adverse event occurred prior to dosing in Period I, two adverse events occurred during Period I, four adverse events occurred during wash-out of period I and two adverse events occurred in Period II. All the adverse events were mild in nature, except for one, which was moderate in nature. All adverse events were resolved. No deaths or serious adverse events were reported during the conduct of the trial.

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

To support this application the applicant submitted one bioequivalence study with a randomised, two-treatment, two-period, two-sequence, single oral dose, crossover design comparing Levetiracetam Accord 1000 mg film-coated tablets with Keppra 1000 mg film-coated tablets in healthy adult human subjects under fasting conditions.

The bioequivalence study was conducted according to the Note for Guidance on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1. The study design, sample size, and statistical methods are appropriate. The 90% confidence intervals of the ratios of geometric means are well in the acceptance range of 80-125% for the primary parameters AUC0-t, AUC0-inf and Cmax for levetiracetam. Bioequivalence can be concluded between Levetiracetam Accord 1000 mg tablets and

Keppra 1000 mg tablets with respect to rate and extent of absorption. The extrapolation to the other dosage strengths is acceptable.

A single dose bioequivalence study is considered sufficient since the application concerns an immediate release formulation. Steady state studies are not indicated as no accumulation is expected, and bioavailability is not affected by repeated doses.

There were no deaths or serious adverse events reported during the conduct of the trial. All adverse events, except for one which was moderate, were mild in nature and resolved. The safety of levetiracetam is well documented and both test and reference products are expected to have a comparable safety profile.

2.4.7 Conclusions on clinical aspects

Based on the presented bioequivalence study Levetiracetam Accord is considered bioequivalent with Keppra.

The results of study BE study n°094-07 with 1000 mg formulation can be extrapolated to other strengths 250, 500, 750 mg, in accordance with 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 for which no safety concerns requiring additional risk minimisation activities have been identified.

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. Additionally, 6-monthly specific safety reports for children below 4 years of age in between the yearly PSURs have to be submitted, until otherwise decided by the CHMP.

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.

The indication of Levetiracetam Accord film-coated tablets is identical to the indication of Keppra film-coated tablets.

From a quality perspective, Levetiracetam Accord 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets contain very similar excipients to Keppra. The quality of the active substance is adequately controlled and all excipients comply with the Ph.Eur. or meet adequate specifications. The finished product manufacturing process shows to be capable of consistently producing tablets that meet the finished product specifications and appropriate packaging is used to ensure the product remains stable within the agreed shelf-life.

No non-clinical studies have been provided for this generic application but an adequate summary of the available non-clinical 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 or 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.

A bioequivalence study with an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover design in healthy adult human subjects 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 the wash-out period was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Levetiracetam Accord 1000 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Keppra 1000 mg film-coated tablets. 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% after single dose administration. Test and reference formulations can be considered as bioequivalent with respect to rate and extent of absorption.

A single dose bioequivalence study was considered sufficient since the application concerns an immediate release formulation. Steady state studies are not indicated as no accumulation is expected, and bioavailability is not affected by repeated doses.

The overall benefit-risk assessment is considered to be positive, since no new indication or population is claimed and reference is made to the innovator product for the benefits and risks of levetiracetam. Levetiracetam is considered a safe and effective antiepileptic drug with well established use for the treatment of various forms of epilepsy, this being supported by experience with marketed levetiracetam in a large number of patients. Thus, the CHMP considered there is sufficient support for concluding on a benefit/risk ratio comparable to the reference product.

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. The information and warnings contained in the product information on the possible adverse effects of levetiracetam are adequate to minimise risk in special patient groups and to ensure the safe administration of levetiracetam. Clinical evidence supports the use of levetiracetam in the treatment of different types of seizures in patients with epilepsy, as listed in the SmPC.

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 Accord in the following indications:

"Levetiracetam 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 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.