19 May 2011
EMA/CHMP/318321/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Levetiracetam ratiopharm

International non proprietary name: levetiracetam

Procedure No. EMEA/H/C/002244

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 ratiopharm GmbH submitted on 30 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam ratiopharm, 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 17 December 2009.

The legal base for this application refers to Article 10 (1) of Directice 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 ratiopharm 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 ratiopharm 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 Keppra.

Film-coated Tablets:

■ 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

■ 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
- Bioavailability study number(s): 299-08

Oral solution:

■ 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 100 mg/ml oral solution
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 29-09-2000
- Marketing authorisation granted by: Community
- Marketing authorisation number: EU/1/00/146/027 and EU/1/00/146/031-032

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

- Product name, strength, pharmaceutical form: Keppra 100 mg/ml oral solution
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 29-09-2000
- Marketing authorisation granted by: Community

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 30 September 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 January 2011 (Annex 4.1).

- 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. (Annex 4.2).
- 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 04 May 2011 (Annex 4.3).

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 ratiopharm.

2. Scientific discussion

2.1. Introduction

Levetiracetam ratiopharm 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets and Levetiracetam ratiopharm 100 mg/ml oral solution are generic medicinal products containing levetiracetam as the active substance.

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 a bioequivalence study at single dose under fasting conditions. The study was performed in healthy volunteers with the 1000 mg tablets.

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

The therapeutic indication of Levetiracetam ratiopharm 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 ratiopharm is presented as film-coated tablets and oral solution. The film-coated tablets contain 250mg, 500mg, 750mg and 1000mg of levetiracetam as active substance. The other ingredients are macrogol, cellulose powdered, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, microcrystalline cellulose, talc and colorants. The medicinal product is packaged in PVC/ Aluminium blisters.

The oral solution contains 100 mg/ml of levetiracetam as active substance. The other ingredients are methyl *para*-hydroxybenzoate, propyl *para*-hydroxybenzoate, acesulfame potassium, grape flavour, citric acid monohydrate, sodium hydroxide and water purified. The solution is packaged in a brown glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing an oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

2.2.2. Active Substance

Levetiracetam is a white to off-white crystalline powder, very soluble in water. It is also freely soluble in chloroform and methanol, soluble in ethanol and sparingly soluble in acetonitrile, and insoluble in n-hexane. It is slightly hygroscopic presenting one single chiral 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.

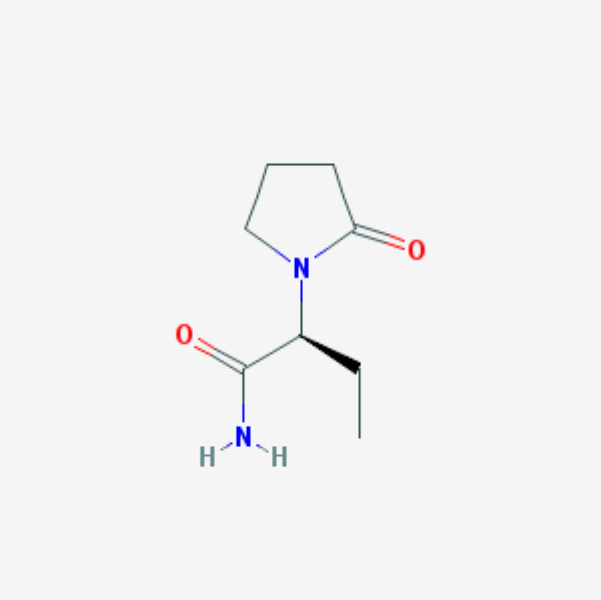

Figure 1: levetiracetam

Manufacture

The Active Substance Master File (ASMF) procedure was followed for the active substance. The manufacturing process of levetiracetam is a four step synthesis followed by purification (crystallisation). A full description of the synthetic route was provided in the restricted part of the ASMF. Adequate controls of critical steps and intermediates are sufficient to ensure the quality of the active substance, and adequate specifications for starting materials, reagents, and solvents have been provided. The purified active substance is packed in two bags of low density polyethylene (one introduced into the other), closed by twisting and fastened with a plastic string. The bags are further packaged in a plastic drum (HDPE) with a plastic cover tightly closed with a metallic devise. 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. The chemical structure of levetiracetam has been confirmed by spectroscopy (IR, 1H-NMR, 13C-NMR, and MS). In addition the molecular weight was determined by elemental analysis.

Specification

Levetiracetam is described in the last edition of the European Pharmacopoeia. The Ph. Eur. specifications have been implemented by both active substance and finished product manufacturers, where applicable, to control the quality of the active substance. The specification also complies with ICH Q3A and includes tests for appearance (visual), identification (HPLC, IR), melting point, loss on drying, chiral purity (chiral HPLC), impurities (HPLC), residue on ignition, heavy metals, particle size, assay (chiral HPLC), residual solvents (GC), water (Ph.Eur.) and appearance of solution. A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable 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 have been provided and show consistent compliance with the predefined active substance specification.

Stability

The stability results from long-term (25°C/60%RH) for 6 production scale batches and accelerated studies (40°C/75%RH) for three production scale batches were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance (visual), melting point, loss on drying, chiral purity (chiral HPLC), impurities (HPLC) and assay (chiral HPLC). It was noticed that the test methods applied are those used for release of the active substance. In can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3. Finished Medicinal Product

Film-coated Tablets

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate a conventional film-coated tablet, with a relatively rapid drug release. containing respectively 250 mg, 500 mg, 750 mg and 1000 mg levetiracetam per tablet and is bioequivalent to the innovator product, Keppra. In this context, the characteristics of the reference product have been studied in terms of its qualitative and quantitative composition along with its physico-chemical properties. The excipients for this particular formulation were selected carefully. It was noted that the excipients selected for this formulation are commonly used in pharmaceutical formulations. Following several studies, the direct compression was selected for manufacturing the film-coated tablets since it is cheaper and demonstrated minor degradation of the active substance while processing. During the pharmaceutical development critical formulation and manufacturing parameters were identified and adjusted. The comparative dissolution profiles were provided. The results demonstrated that the generic batches used for the bioequivalence studies and the EU brand leader batches are similar with respect to dissolution rate.

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. The excipients used 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 proposed commercial manufacturing process for the film-coated tablets involves standard technology and it is divided into the following steps: mixing, sieving, homogenization and addition of outer phase, compression, film coating, filling and packaging. The equipment used is commonly available in the pharmaceutical industry. The manufacturing process has been adequately described and some steps have been identified and control, but they are not considered as critical. It was noticed that the manufacturing process has been adequately validated for one pilot batch of each strength and from each manufacturing site. 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

The product specification is standard for film-coated tablets and contains tests with suitable limits for appearance, uniformity of dosage (Ph.Eur), resistance to crushing (Ph.Eur), subdivision of tablets (Ph.Eur), identification of titanium dioxide (Ph.Eur), identification of iron oxide (Ph.Eur), identification (HPLC and UV), assay (HPLC), impurities (HPLC) and microbiological purity (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for 2 pilot batches of each strength from each manufacturing site confirm that the film-coated tablets can be manufactured reproducibly according to the agreed finished product 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 impurities. The analytical methods used for the stability studies are identical with the methods proposed for routine testing of the finished product. During the stability studies the product did not show any significant change in its 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.

A Photostability testing program was conducted on one batches (250 mg) in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Oral Solution

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate an oral solution (levetiracetam 100 mg/ml) essentially similar to the reference product Keppra, 100 mg/ml oral solution and with a good taste and compliance. Therefore, the characteristics of the reference product have been studied in terms of its qualitative and quantitative composition along with its physico-chemical properties. The excipients for this particular formulation were selected carefully and compatibility studies were conducted. It was noted that the excipients selected for this formulation are commonly used in pharmaceutical formulations and quite similar to the reference product, with exception of two excipients. The preservative system was selected following the results of the microbial test, which were performed in accordance with Eur. Ph. It was noted that the pH of the oral solution was selected to guarantee the stability of the active substance, finished product and the efficacy of the preservatives.

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. The excipients used 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 proposed commercial manufacturing process for the oral solution involves standard technology and it is divided into the following steps: mixing, heating, stirring, cooling, pH adjusting, filtration, bottle filling and capping. The equipment used is commonly available in the pharmaceutical industry. The manufacturing process has been adequately described and some steps have been identified and control, but they are not considered as critical. It was noticed that the manufacturing process has been adequately validated for two pilot batches a validation protocol proposed for three consecutive batches has been provided.

Product Specification

The product specification is standard for oral solutions and contains tests with suitable limits for appearance, odour, filling volume, pH, identification of methyl para-hydroxybenzoate, propyl para-hydroxybenzoate and levetiracetam, assay of para-hydroxybenzoate, propyl para-hydroxybenzoate and levetiracetam, impurities (HPLC), identification of plastic materials (IR) and microbiological purity

(Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product 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 four pilot batches.

The results of the following tests were submitted: appearance, odour, pH, assay of para-hydroxybenzoate, propyl para-hydroxybenzoate and levetiracetam, impurities (HPLC) and microbiological purity (Ph.Eur).

The analytical methods used for the stability studies are identical with the methods proposed for routine testing of the finished product. During the stability studies the product did not show any significant change in quality. All the results remained well within the specification limits during all the stability studies.

In-use stability studies were performed on the two pilot scale batches of Levetiracetam 100 mg/ml oral solution packaged in 300 ml glass bottles. The batches were stored under long-term ICH storage conditions at (25°C/60%RH). All results were in compliance with the specification requirements.

A Photostability testing program was conducted on one batches in accordance with the recommendations of ICH guideline Q1B The results were found to meet the specifications and the finished product does not require any special light protection.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

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 both the active substance and the finished product manufacturers are in-line with the monograph.

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at pilot scale at the proposed manufacturing site. The validation protocol proposed for the full scale batches has been provided for both pharmaceutical forms. 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.

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

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

The container-closure systems for both pharmaceutical forms were 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 finished were adequately established.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished products 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 medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

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 ratiopharm manufactured by ratiopharm GmbH 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 abridged application for film-coated tablets, and oral solution containing levetiracetam. To support the marketing authorisation application the applicant conducted one 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 film-coated tablets and oral solution 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 clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The contract research organisation has been inspected by competent authorities over the period between 2004 and 2009 and was found compliant with ICH GCP requirements.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study (BE study n°299-08).

2.4.2. Pharmacokinetics

Methods

Study design

The study was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study of Levetiracetam ratiopharm 1000 mg film-coated tablets in comparison with Keppra 1000 mg film-coated tablets in healthy adult human subjects under fasting conditions. The study was conducted by a by a contract research organisation based in India between 17 and 24 December 2009.

Twenty-eight subjects were administered a single dose of either the test or reference (Keppra) study medication, as a 1 x 1000 mg tablet with 240 mL of low carbonated water after an overnight fast of at least 10 hours. Subjects were instructed to remain in sitting or ambulatory posture for the first 3 hours after dose administration. This was a randomised study design. The order of receiving the test product-B and the reference product-A for each subject during both the periods of the study was determined according to the randomisation schedule.

The sampling schedule was planned to provide a reliable estimate of the extent of absorption. 23 blood samples were collected from each subject during each period to analyse the pharmacokinetic profile of the test as well as the reference drug. The samples were collected prior to drug administration and at 0.167, 0.33, 0.50, 0.67, 0.83, 1.00, 1.167,1.333, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours following the drug administration in each period. Samples at 36 hours were collected on ambulatory basis. A washout period of 5 days was maintained between the successive dosing days.

Test and reference products

Levetiracetam ratiopharm 1 x 1000 mg tablet has been compared to Keppra 1 x 1000 mg tablet manufactured by UCB Pharma S.A., Belgium, (Batch No: 47653. Expiry date: March 2011).

Population(s) studied

The sample size was determined based on an intra-subject bioequivalence variability of approximately 18%, a T/R ratio of 95-105%, a significance level of 5%, a power of > 80% and bioequivalence limits of 80-125%. Based on the above estimates, a sample size of 24 subjects was considered to be sufficient to establish bioequivalence with adequate power. To allow for dropouts and withdrawals, 28 subjects were considered to be sufficient.

A total of 30 subjects, including 2 extra subjects, were recruited for Period I. They were healthy adult, human volunteers between 18 - 55 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5- 24.9 (both inclusive) and living in the western part of India. Out of these, 28 subjects were dosed. The remaining two subjects left the study prior to dosing.

23 out of 28 subjects completed the study. One subject was withdrawn from the study on medical grounds (drowsiness) in period I. Another subject was withdrawn from the study on medical grounds (Throat pain and Swallowing difficulty) before dosing in Period II. Three more subjects were withdrawn from the study in Period II (emesis and drowsiness). Plasma samples of all the 23 subjects were analysed. In addition and based on protocol requirements, study samples of subjects withdrawn on medical grounds were also analysed.

Analytical methods

The bioanalytical analysis was performed at the bioanalytical department of the contract research organisation between December 2009 and January 2010.

The bioanalytical report (project n° 299-08) and the validation of method for the determination of levetiracetam in human plasma using LC-MS/MS (MV-284-09) were provided in the dossier. The plasma concentrations of levetiracetam in the study samples were quantified by a validated LC-MS/MS method. Concerning the validation of the bioanalytical method, information on the linearity, accuracy and precision, recovery, selectivity, sensitivity, matrix effect, short and long term stability was provided. The analytical method used was shown to be sensitive, accurate and selective for the plasma level determination of levetiracetam in the concentration range of 0.250-40.122 µg/mL. The lower limit of quantification (LLOQ) was 0.250 µg/mL. Concentrations below the lower limit of quantification have been considered non-quantifiable. Long term stability data of plasma samples for 82 days were generated and reported in the dossier.

A total of 1176 samples were analysed during the study. A total of 20 reanalyses were carried out due to the following reasons:

• Fourteen samples were re-analysed due to concentration above the highest standard.

• Three samples were reanalysed due to significant variation in response of internal standard.

• Two samples were reanalysed due to anomalous concentration.

• One sample was reanalysed as significant drug and internal standard response was observed at the retention time and transition of drug and internal standard, which might be due to contamination of particular sample vial.

Consequently, the applicant was requested by the CHMP to discuss the criteria for the re-analysis of some of the samples. In their response the applicant clarified that reasons for performing the reanalyses were not related to pharmacokinetics. Moreover, it was shown that the re-calculation of the PK parameters using the original values for these samples had no influence on the conclusions on bioequivalence. The CHMP found the applicant's responses acceptable.

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).

The following standard PK parameters were calculated: peak plasma concentration (Cmax), time to Cmax (Tmax), areas under the concentration-time curve from 0 to last measurable concentration (AUC0-t) and area extrapolated to infinity (AUC0-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 of Cmax, AUC0-t and AUC0-inf were computed 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).

The 90% parametric confidence intervals were calculated for the un-transformed and ln-transformed pharmacokinetic parameters of Cmax, AUC0-t and AUC0-inf.

Bioequivalence of test product vs. reference product was concluded, if the 90% confidence interval fell within the acceptance range of 80-125% for ln-transformed pharmacokinetic parameters Cmax and AUC0-t.

Results

The results of the study are presented in table below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

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	304 ± 47	315 ± 50	31 ± 6	0.833	7.41 ± 0.88
Reference	302 ± 45	314 ± 49	32 ± 8	0.500	7.55 ± 0.89
*Ratio (90%CI)	101 (99–102)	100 (99–102)	97 (92–102)	-	-
CV (%)	3.3	3.5	10.6	-	-

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

*ln-transformed values

The 90% confidence intervals 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 ratiopharm 1000 mg tablets and Keppra 1000 mg tablets can be considered as demonstrated.

Safety data

A total of 26 adverse events were reported by 16 subjects during the conduct of the study. Out of these, 13 adverse events occurred during Period I, and 13 adverse events occurred during Period-II. Most of the adverse events were mild in nature and the subjects were followed up till resolution. The relationships of six adverse events in the reference group and 16 adverse events in the test group were judged as possible to the study drug. The relationships of one adverse event in the reference group and three adverse events in the test group were judged as unlikely to the study drug. There were four adverse events considered as significant: throat pain and swallowing difficulty and 2 cases drowsiness. The first two were considered to be unlikely and the latter two were considered to be possible in relationship to the study drug. All of those adverse events resolved without any sequelae. There were no deaths or SAE reported.

Exemption

Four different strengths of levetiracetam tablets (250, 500, 750, 1000 mg) have been developed by the MAH. The application for all the dosage strengths is based on the bioequivalence study with levetiracetam 1000 mg film-coated tablets, ratiopharm GmbH.

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:

a) The product levetiracetam 250 mg, 500 mg, 750 mg & 1000 mg film-coated tablets 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% occurs after 15 minutes;

e) Levetiracetam shows linear pharmacokinetics over the therapeutic range.

Based on the aforementioned "Guideline on the Investigation of Bioequivalence", bioequivalence testing for levetiracetam 100 mg/ml oral solution should not be required, providing:

a) it is an aqueous oral solution at time of administration which contains an active substance in the same concentration as the reference product (Keppra, 100 mg/ml oral solution manufactured by UCB Pharma SA, Belgium);

b) the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance.

It was noted by the CHMP that Levetiracetam ratiopharm 100 mg/ml oral solution did not contain glycerol and maltitol unlike Keppra oral solution. Although the impact of excipients in immediate

release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (BCS-class I) was considered unlikely, it was felt that it could have not been excluded.

Therefore, the applicant was asked to discuss the discrepancy in excipients between the Keppra oral solution and the intended oral solution and its impact on gastrointestinal motility and levetiracetam bioavailability. In their responses the applicant pointed out that levetiracetam is rapidly and almost completely (>95%) absorbed following oral administration of tablet doses ranging from 250 mg to 5000 mg, it is minimally metabolised and only 0.3-1% of the administered dose is excreted with faeces. Moreover, a phase I PK study confirmed that a 10% oral solution of the reference product Keppra was bioequivalent to the 750 mg tablet providing additional reassurance that excipients in Keppra did not influence the bioavailability of the oral solution. Consequently, the CHMP considered that the applicant provided sufficient justification that the discrepancy in excipients between both products would have no impact on bioequivalence.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

N/A

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 classic randomised, two-treatment, two-period, two-sequence, single oral dose, crossover design comparing Levetiracetam ratiopharm 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 were appropriate. The 90% confidence intervals of the ratios of geometric means were in the acceptance range of 80-125% for the primary parameters AUC0-t, AUC0-inf and Cmax for levetiracetam. Formulation, period and sequence effects were found to be statistically insignificant at 5% significance level for all PK parameters. The inter- and intra-patient variability was low due to the high bioavailability, predominantly renal excretion and lack of pharmacokinetic interactions. Therefore, bioequivalence was concluded between Levetiracetam ratiopharm 1000 mg tablets and Keppra 1000 mg tablets with respect to rate and extent of absorption. The extrapolation to other dosage strengths was found to be acceptable. Bioequivalence testing for levetiracetam 100 mg/ml oral solution was not

required as the requirements of the "Note for Guidance on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1" were considered to be fulfilled.

There were no deaths or SAE reported. The safety of levetiracetam is well documented and both test and reference products are expected to have a comparable adverse drug reaction profile.

2.4.7. Conclusions on clinical aspects

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

The results of study BE study n°299-08 with 1000 mg formulation can be extrapolated to other strengths 250, 500, 750 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

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.

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 application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

Routine pharmacovigilance activities according to volume 9A of the NtA 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.

2.6. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable since the package leaflet of this generic application is identical to the reference product except for the product name.

2.7. Benefit-Risk Balance

This application concerns a generic version of levetiracetam film-coated tablets and oral solution. 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.

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 wash-out period was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Levetiracetam ratiopharm 1000 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with 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%. Bioequivalence of the two formulations was demonstrated.

Based on the "Note for Guidance on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1", bioequivalence testing for levetiracetam 100 mg/ml oral solution was waived.

A benefit risk balance 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.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the risk-benefit balance of Levetiracetam ratiopharm as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy and as adjunctive therapy in 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.