EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July2011
EMA/CHMP/323600/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Matever

International nonproprietary name: levetiracetam

Procedure No. EMEA/H/C/2024

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 Pharmathen S.A. submitted on 30 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Matever, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2009

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:

- 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.

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.

Information on Paediatric requirements

Not applicable

Information relating to Orphan Market Exclusivity

Not applicable.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Keppra 250 mg film-coated tablets
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 29 September 2000
- Marketing authorisation granted by: Community
  - Community Marketing authorisation numbers:

EU/1/00/146/001
EU/1/00/146/002
EU/1/00/146/003
EU/1/00/146/004
EU/1/00/146/005
EU/1/00/146/029

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

- Product name, strength, pharmaceutical form: Keppra 250 mg film-coated tablets
- Marketing authorisation holder: UCB Pharma SA
- Date of authorisation: 29 September 2000
- Marketing authorisation granted by: Community
  - Community Marketing authorisation numbers:

EU/1/00/146/001
EU/1/00/146/002
EU/1/00/146/003
EU/1/00/146/004
EU/1/00/146/005
EU/1/00/146/029

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

- Product name, strength, pharmaceutical form: Keppra 1000mg film-coated tablets
- Marketing authorisation holder: UCB Belgium SA
- Date of authorisation: 29 September 2000
- Marketing authorisation granted by: Community
  - Community Marketing authorisation numbers:

EU/1/00/146/020
EU/1/00/146/021
EU/1/00/146/022
EU/1/00/146/023
EU/1/00/146/024
EU/1/00/146/025
EU/1/00/146/026

  - Member source: EL
- Bioavailability study number: Study Code LVA-P5-042

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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dalibor Valik Co-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 07 January 2011.
- During the meeting on 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 21 February 2011.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 March 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 April 2011.
- During the CHMP meeting on 19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 June 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 07 July 2011.
- During the meeting on 18-21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Matever on 21 July 2011.

2 Scientific discussion

2.1 Introduction

Matever presented as film-coated tablets and concentrate for solution for infusion is a generic medicinal product of Keppra containing the active substance levetiracetam.

The applicant initially applied also for the oral solution but withdrew this pharmaceutical form during the evaluation process.

The reference medicinal product is Keppra as film-coated tablets, oral solution and concentrate for solution for infusion 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.

Bioequivalence to the reference product was demonstrated by one bioequivalence study at single dose under fasting conditions with the 1000 mg tablets. The studies were performed in healthy volunteers.

The indication proposed for Matever is identical to the indication of the reference medicinal product, as follows:

- 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

The proposed products Matever 250 mg, 500 mg, 750 mg, 1000 mg are immediate release film-coated tablets, and Matever 100 mg/ml concentrate for solution for infusion containing Levetiracetam as the active substance. The dosage forms have been developed as a generic product to the centrally authorized product Keppra containing the same active substance and the same pharmaceutical forms.

The tablets are packed in PVC/PE/PVdC//Al blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 80, 100, 120, 200 film-coated tablets.

The concentrate for solution for infusion is packed in glass vial with bromobutyl rubber stopper and aluminium cap.

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.

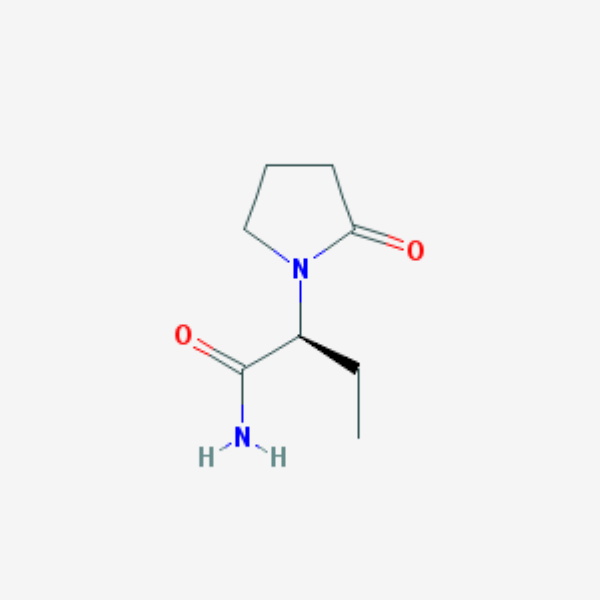

Figure 1: Chemical structure of levetiracetam

Manufacture

The active substance levetiracetam has followed the Active Substance Master File (ASMF) procedure.

The Manufacturer of the active substance has submitted a complete ASMF and the Applicant's part has been included in the dossier.

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

A full description of the manufacturing was provided in the restricted part of the ASMF.

Confirmation of the chemical structure of levetiracetam was provided by elemental analysis, mass spectrum, ^{1}H NMR, ^{13}C NMR spectrometry, IR and UV spectrophotometry. The physicochemical properties have been determined using X-ray powder diffractometry (XRPD) and demonstrated the absence of polymorphism.

Specification

Levetiracetam is described in the last edition of the European Pharmacopoeia (Ph. Eur.). The Ph. Eur. monograph specifications have been implemented by both active substance and finished product manufacturers, where applicable, to control of the active substance.

Adequate specification used by the finished product manufacturer includes the following parameters to be tested: description (visual), solubility, identification (IR and HPLC), specific optical rotation, water content, sulphated ash, heavy metals, assay (HPLC), related substances (HPLC), residual solvents (GC), chiral purity (R-isomer, HPLC), microbiological quality.

Justification of the specification has been provided and the limits for the related substances and residual solvents do not raise any toxicological concern and comply with the ICH guidelines.

Analytical methods used by the finished product manufacturer have been satisfactorily described and where needed validated in accordance with ICH requirements.

Batch analysis data for three recent batches manufactured by both manufacturing sites using the current synthesis are presented. All batches comply with the specification.

Stability

Stability studies of three registration batches kept in the commercial packaging have been provided under ICH conditions long term (24 months at 25°C/60%RH) and accelerated (6 months at 40°C/75%RH). The following parameters were tested: description, loss on drying, related substances, assay, R-isomer, levetiracetam acid and the analytical methods were those used for the control of the active substance.

Forced degradation and photostability studies in line with ICH guidance have been conducted. Based on the results of assay and chemical purity it was concluded that levetiracetam was photostable.

2.2.3 Finished Medicinal Product

Film-coated tablets

The film-coated tablets consist of 4 strengths: 250 mg, blue, oblong, biconvex film-coated tablets; 500 mg, yellow, oblong, biconvex film-coated tablets; 750 mg, pink, oblong, biconvex film-coated tablets, 1000 mg: white, oblong, biconvex film-coated tablets.

The ingredients for the core tablets include: levetiracetam (active substance), calcium hydrogen phosphate dehydrate (diluent), cellulose microcrystalline (diluent), crospovidone type A (disintegrant), hydroxypropylcellulose (binder).

For the film-coating of the 250 mg the ingredients are: Opadry 02H20569 (blue): hypromellose (E464), titanium dioxide (E171), talc, propylene glycol (E1520), indigo carmine aluminium lake (E132), sunset yellow FCF aluminium lake (E110), quinoline yellow aluminium lake (E104).

For the film-coating of the 500 mg the ingredients are: Opadry 20J22730 (yellow): hypromellose (E464), titanium dioxide (E171), hydroxypropyl cellulose (E463), propylene glycol (E1520), quinoline yellow aluminium lake (E104), sorbic acid (E200), sorbitan monooleate (E494), vanillin.

For the film-coating of the 750 mg the ingredients are: Opadry OY-S-33016 (orange): hypromellose (E464), indigo carmine aluminium lake (E132), sunset yellow FCF aluminium lake (E110), iron oxide red (E172), macrogol/PEG 4000, titanium dioxide (E171).

For the film-coating of the 1000 mg the ingredients are: Opadry OY-LS-28908 (II white): hypromellose (E464), lactose monohydrate, macrogol/PEG 4000, titanium dioxide (E171).

The tablets are packed in PVC/PE/PVdC//Al blisters.

Concentrate for solution for infusion

The concentrate for solution for infusion is a clear, colorless, sterile solution (500 mg/ 5 ml), free from foreign particles.

The product contains levetiracetam as the active substance and the following excipients: sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injection.

The concentrate for solution for infusion is packed in a transparent 7 ml type I glass vial with rubber stopper and aluminium flip cap. The vials are packed in cardboard boxes with 10 vials inside.

Pharmaceutical Development

Film-coated tablets

The tablets have been developed with the objective of developing a conventional release film coated tablets bioequivalent with the innovator's product Keppra tablets.

Compatibility studies were performed to ensure that the active substance does not degrade in the presence of the excipients being together in the core. Results of HPLC analysis did not show interaction between the active substance and the excipients and this was further confirmed by stability data of the finished product.

Due to the high content of levetiracetam in the tablets the bulk has limited flow properties, thus wet granulation was chosen for the manufacturing process. Thermal behaviour, compression characteristics were investigated and the product shows degradation under light, heating, acid, alkaline or oxidative treatment.

Standard common excipients have been chosen for the tablets. All excipients are pharmacopoeial excipients. Only for some colorants used for the coating in-house specification has been proposed. No novel or unusual excipients were used.

The formulation development was satisfactorily described. Compared to the innovator formula, starch maize was replaced with calcium hydrogen phosphate dihydrate due to its better compressibility. Sodium starch glycolate was included as a disintegrant to have the optimum properties. The binder was hydroxypropylcellulose and its choice was extensively explained.

The development of discriminative dissolution method (to the changes of the product formulation) has been described. The development was based on Keppra 1000 mg. The media tested were 0.1 N HCl, buffer pH 4.5, buffer pH 6.8, water. The results showed that the product is highly soluble in all media; finally 0.1 N HCl was selected as the dissolution medium in order to simulate the gastric environment in which the tablet is diluted when administered. Dissolution profiles of three batches of Matever 1000 mg confirmed the adequacy of the method.

Dissolution profiles of the bio-batch and several batches of the tested product and the reference products from different European countries have been submitted. The dissolution profiles of tested and reference products 250 mg, 1000 mg and of tested products 250, 500, 750, 1000 mg were similar in all three media (more than 85% within 15 min). The dissolution was found pH dependent; however, taking into account the results from dissolution studies and bioequivalence study, this has no major impact on the in vivo performance of the finished product.

A Biowaiver has been accepted for the 250 mg, 500 mg, 750 mg strengths: All strengths are manufactured by the same process, the core composition is proportionally linear, the PK is linear in the therapeutic range, and the dissolution profiles of all strengths in the three media were very rapid. Therefore the biowaiver for the lower strengths was accepted.

The impurities profile of Keppra from different European Countries has been compared with Matever for all strengths and showed similar results.

The Bioequivalence Study for the 1000 mg strength can be found in detail in the Clinical section.

The choice of the container was a white opaque PVC/PE/PVDC combined with aluminium foil blisters. The packaged product was tested on acceptability in accelerated and long term stability.

Oral solution

In the initial application, an oral solution was developed for patients who cannot swallow film-coated tablets and for younger paediatric patients to ensure acceptability and flexibility of dosage. During the evaluation procedure, the CHMP requested additional syringes used for the administration of the oral solution and data on the accuracy of the syringes, as well as more information on impurities for the active substance. The applicant decided not to go ahead with this pharmaceutical form and decided to withdraw the oral solution before the Opinion. This was accepted.

Concentrate for solution for infusion

The concentrate for solution for infusion has been developed with the objective of developing a pharmaceutical form similar to the innovator's product Keppra concentrate for solution for infusion

The formulation development was based on the originator, and Matever contains the same excipients (qualitatively) as in Keppra parenteral formulation.

Matever has been compared with Keppra from several Member states, and similar results were found for impurities, assay, enantiomeric purity and osmolality, specific gravity, pH.

The manufacturing process has been adequately described.

The choice of the container was a transparent 7ml type I glass vial, sealed with a rubber stopper and aluminium flip cap. The package was tested on acceptability and during long term stability.

Compatibility study of Matever concentrate in Dextrose 5%, Lactated Ringer solution and in NaCl 0.9 %, all in PVC bags has been provided.

Furthermore the compatibility study of Matever concentrate in the same solutions stored at 2 – 8 °C for 24 hours has been carried out. Testing was for appearance, color of solution, pH, particulate matter, assay and related substances. Results showed that Matever diluted in each of the parenteral solutions stored at room conditions 2 - 8 °C is stable for at least 24 hours.

Adventitious agents

Film-coated tablets

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

BSE/TSE Statements for the excipients are provided in Module 3.2.R. The products do not contain and are not derived from any category A or B as defined in the TSE guideline (EMEA/410/01 rev.2)

Opadry white contains lactose monohydrate considered a category C material which indicates no detectable infectivity. The lactose has been prepared according to the description given in EMEA/CPMP/571/02 with no risk anticipated. This is acceptable.

Concentrate for solution for infusion

All excipients used for the concentrate for solution for infusion comply with the provisions of Commission Directive 2001/83/EC as amended and with Chapter "5.2.8. Minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" of the Ph. Eur. BSE/TSE Statements for the excipients are provided in Module 3.2.R.

Manufacture of the product

Film-coated tablets

The manufacturing process for the film-coated tablets can be summarized as follow and considered as standard: weighing and sieving of the raw materials, mixing with internal phase excipients, wet granulation, drying of the granulate, second mixing with the external phase ingredients, compression, coating, packaging.

Satisfactory flow-chart with In-Process Controls (IPCs) of the manufacturing process has been included. In addition, the narrative description of the process has been provided and includes such details as sieve opening sizes, temperatures, blending times etc. The list of IPCs such as compression, coating, packaging performed during the manufacture of the film-coated tablets has been provided. It contains satisfactory details such as tested parameters, methods used, limits and frequency of testing.

A satisfactory validation study has been provided for three pilot batches of Matever 250, 500, 750, 1000 mg film-coated tablets. 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.

All excipients employed in the manufacture of the tested product comply with the requirements of the relevant Ph. Eur. Monograph except for the coating agents which are controlled according to in-house specifications. The colorants comply with the EC Directive on colorants to be used in foodstuffs 95/45/EC as amended.

The compendial methods are applied for the tests described in the Ph. Eur. monograph. Validations of the analytical methods employed are not required. Description and validation of in-house methods have been provided in line with ICH requirements.

The pharmacopoeial specifications do not require any justification since the excipients are used in an usual dosage form and in widely used function. Satisfactory Certificates of analysis have been provided.

Concentrate for solution for infusion

The manufacturing process can be summarized with the following steps: Weighing of raw materials and Volumetric determination of water for injection, Preparation of the Levetiracetam solution, aseptic filtration, filling and sealing of the vials, final sterilization. Satisfactory flow-chart with In-Process Controls of the manufacturing process including tests such as appearance, filter integrity, and pH has been included:

In addition, the narrative description of the process has been provided and includes details such as cleaning times and pressure, temperatures. The sterilization process is performed in an autoclave. The product is end sterilized at 121°C for 20mins in the presence of a sterilization indicator. Filter validation data as well as steam sterilization validation are submitted. The list of process controls performed during the manufacture of the concentrate has been provided. It contains satisfactory details such as tested parameters, methods used, limits and frequency of testing.

The validation of the manufacturing process has been evaluated on three consecutive production scale batches. The quality of the production batches was evaluated through the results of in process testing as well as the results of finished product testing. The validation protocol was enclosed in the dossier.

All excipients employed comply with the requirements of the relevant Ph. Eur. monograph.

The compendial methods were applied for the tests described in the Ph. Eur. monograph. Therefore validations of the analytical methods employed were not required

The pharmacopoeial specifications do not require any justification, as the excipients are used in an usual dosage form and in widely used function. Satisfactory Certificates of analysis of all excipients have been provided.

Product Specification

Film-coated tablets

The proposed release and shelf life specifications include the following parameters: appearance (visual), identification (UV and HPLC), average mass (PhEur. 2.9.5), uniformity of mass (PhEur. 2.9.5), uniformity of dosage units (mass variation PhEur 2.9.40), loss on drying (PhEur.2.2.32), hardness (Ph.Eur.), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), disintegration (Ph.Eur. 2.9.1), dissolution (in-house method), identification of colorants (in-house method), microbial contamination (PhEur 2.6.12, 2.6.13), residual solvents (GC), blister tightness (visual), packaging (visual).

The release and shelf life limits of the active substance content are in line with batch and stability data. The limits for microbial contamination are in line with Ph Eur requirements for solid per orally administered products and accepted. Limits for related substances and residual solvents are in line with ICH limits and do not raise any specific toxicological concern.

The analytical methods were adequately detailed and the non-compendial methods were validated in accordance with ICH guidelines.

Batch data were provided for three batches of each strength. All presented batches comply with the proposed specifications and demonstrate consistent manufacture.

The primary packaging is a blister consisting of white PVC/PE/PVdC foil and aluminium foil. Blisters are packed in cardboard cartons.

The bulk tablets are packed in double PE bags in opaque plastic container protected from light.

The specifications for both parts of blisters have been provided and are satisfactory. The test methods have been described and acceptable certificates of analysis are provided. The copies of IR spectra for materials have been provided

The blister components comply with the actual requirements of the Ph. Eur., the Commission Directive relating to plastic materials and articles intended to come into contact with foodstuffs and relevant EU regulations.

Concentrate for solution for infusion

The proposed release and shelf life specifications include the following parameters: appearance (visual), foreign particles (visual), average volume and volume variation (Ph.Eur), pH (Ph.Eur), osmolality (Ph.Eur), specific gravity (Ph.Eur), osmolality (Ph.Eur), identification (UV and HPLC), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), uniformity of dosage units (Ph.Eur. 2.9.40), particulate contamination (2.9.19), sterility (Ph.Eur. 2.6.1), endotoxin test (Ph.Eur. 2.6.14), air/water tightness.

The proposed specifications at release and end of shelf life are generally acceptable. The release and shelf life limits of the active substance content are in line with batch and stability data. Sterility and bacterial endotoxin tests are in line with Ph. Eur. requirements.

Description and validation of the methods are acceptable.

Batch data were provided for three production-scale batches. The results complied with the proposed specifications and demonstrate consistent manufacture.

Matever concentrate is packed in 7 ml, type I transparent glass vial complying with Ph. Eur. requirements on high hydrolytic resistance suitable for use in parenteral preparation. The vials are sealed with bromobutyl rubber stopper 20 mm (type I of Ph. Eur. 3.2.9) and an aluminium flip cap 20 mm.

The specifications for vial, rubber stopper and cap have been provided and are satisfactory. The test methods have been described and acceptable certificates of analysis are provided. It was confirmed that elastomeric closures (bromobutyl compound with silicate filler and inorganic colouring system) do not contain PVC. Elution test of stoppers has been performed with acceptable results.

The plastic container components comply with the actual requirements of the Ph. Eur., the Commission Directive relating to plastic materials and articles intended to come into contact with foodstuffs and relevant EU regulations, where applicable. The copies of IR spectra for materials have been provided.

Stability of the product

Film-coated tablets

Stability studies were carried out on three batches of each strength in line with ICH guidelines. The product was tested under long-term conditions (36 months at 25°C / 60% RH), intermediate conditions (36 months at 30°C / 65% RH) and accelerated conditions (6 months at 40°C / 75% RH). The product was kept in the commercial blister packaging.

The results of the following tests were submitted: appearance, identification, average mass, hardness, loss on drying, assay, related substances, disintegration, dissolution, microbial contamination, tightness of blister.

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

During the stability studies the product did not show any significant change in the quality.

All the results remained well within the specification limits during all the stability studies.

Results for bulk stability studies of all strengths were also acceptable. The Bulk shelf life of 6 months is acceptable when stored below 25 °C.

Forced degradation study data show that the product is not sensitive to light or moisture in the commercial package.

Based on the data, the shelf life when used in the conditions defined in the SmPC can be accepted

Concentrate for solution for infusion

Stability studies were carried out on three production-scale batches of Levetiracetam concentrate kept in the commercial packaging. The studies were conducted under ICH conditions namely under long-term conditions (12 months at 25°C / 60% RH), intermediate conditions (12 months at 30°C / 65% RH), accelerated conditions (6 months at 40°C / 75% RH)

The analytical methods used for the stability studies were identical to the methods proposed for routine testing of the finished product as mentioned section 3.2.P.5.1. The methods for assay and related substances were proven during their validations as stability-indicating. The following tests were investigated: Appearance, identification, pH, average volume, optical control, specific gravity, osmolality, assay of levetiracetam, related substances, enantiomeric purity, air/water tightness of vials, endotoxin test, sterility and particulate contamination.

An in-use stability study for 24 hours has been performed after first opening for dilution. It was concluded that the results of the in-use stability testing remain within the proposed limits for the control tests and the Levetiracetam concentrate are therefore found to be stable.

The shelf-life is accepted when used in the conditions defined in the SmPC.

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 and a validation protocol has been presented.

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

Batch analyses 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 confirmed by the stability data.

The stability studies comply with the ICH stability guideline. The control tests and specifications for the finished product 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 for both pharmaceutical forms (film coated tablet and concentrate for solution for infusion), 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 Matever manufactured by Pharmathen S.A. 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.

2.4 Clinical Aspects

2.4.1 Introduction

This is an abridged application for film-coated tablets and concentrate for solution for infusion containing Levetiracetam. To support the marketing authorisation application for the film-coated tablets, the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment. No studies have been conducted with the concentrate for solution for infusion.

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

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

GCP

The clinical trial was performed in accordance with GCP as claimed by the applicant.

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

Exemption

Film-coated tablets

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

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

a) Matever tablets are manufactured by the same manufacturing process,

b) The qualitative composition of Matever tablets is the same for all strengths included in the marketing authorization application,

c) The ratio between the amounts of excipients is similar for all strengths included in the marketing authorization application,

d) Dissolution profiles are similar under identical conditions for the additional strengths and the strengths of the batches used in the bioequivalence study.

e) Levetiracetam has shown to display linear pharmacokinetics over therapeutic range

Concentrate for solution for infusion

One strength of Levetiracetam 100mg/ml concentrate for solution for infusion (500mg/5ml) has been developed by the MAH. No formal bioequivalence study was submitted and a biowaiver was requested.

This approach is considered acceptable as it is in line with conditions set forth in the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.:*

a) Matever concentrate for solution for infusion is a parenteral solution

b) Pharmaceutical equivalence testing has illustrated that Matever concentrate for solution for infusion is essentially similar to the reference product, Keppra 100mg/ml concentrate for solution for infusion (500mg/5ml), in terms of the active content and assay of related substances.

Clinical studies

Film-coated tablets

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

- Study LVA-P5-042 is a single dose (under fasting conditions) trial. This study has investigated the 1000 mg strength.

Concentrate for solution for infusion

Not applicable

2.4.2 Pharmacokinetics

Methods

Study design

The study was a single centre, randomised, single dose, laboratory-blinded, two-period, two-treatment, two-sequence, crossover study, performed under fasting conditions in healthy volunteers (males and females).

Each subject received a single dose of respective formulation in each period with 240 ml of water after an overnight fast. Each treatment was administered once according to a randomisation list. Standardised meals were served during each study phase.

The minimum wash-out period was 7 days.

Blood samples were collected predose (0), and up to 36 hours after drug administration at 0.17, 0.33, 0.5, 0.67, 0.84, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours post-dose in K_3 EDTA Vacutainers. After centrifugation, the plasma samples were transferred into the labelled polypropylene tubes in two splits and frozen on dry ice, than stored at -20ºC until sent to the laboratory for assay.

The clinical part of the study was performed from 22.10.2005 to 31.10.2005 a Clinical Research Organisation (CRO) in Canada (clinical part and analytical part).

Statement of compliance with GCP and GLP is presented.

Study was approved on 15 Sep 2005 by the Ethical committee composed according to the ICH standards.

The study itself has not been inspected, however, the clinical and analytical sites were inspected by EU authorities: by AFSSAPS in November 2003 and by MHRA in October 2007 respectively. No critical findings were found,

The CHMP considers that the design of the study is appropriate. The wash out period satisfies criteria of at least 5-times the half life (T1/2 being ca 7h), thus it is sufficient; the sampling time schedule is deemed adequate in order to estimate Levetiracetam PK parameters.

Test and reference products

Matever 1000 mg film coated tablet manufactured by Pharmathen S.A. (batch No. 078025…, manufacturing date 10/2005) has been compared to Keppra 1000 mg film coated tablet manufactured by UCB Pharma S.A., Belgium (Batch No: 0000005264, exp. Date 03/2008).

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

The certificates of analysis for both the test and reference products were presented. The batch size of the test product was declared and considered adequate. The dose (1000 mg) corresponds to the highest strength applied for.

Population studied

Thirty-two (28 + 4 alternates) healthy, non-smoker/ex-smokers or light smokers (no more than 10 cigarettes per day), male and female subjects were randomized into the study. No subject dropped out from the study.

Thus, thirty-two (32) subjects completed both study periods.

In accordance with the protocol, only the samples of the first 14 subjects assigned to each sequence of drug administration (i.e.: 28 subjects) were analysed and included in the PK evaluation.

Mean age (± SD) of the thirty two subjects (17 men and 15 women) was 34 ± 10 years; mean height 168.2 ± 8.4 cm; mean weight 68.8 ± 9.1 kg; and mean BMI 23 ± 2 kg/m2.

All subjects were Caucasians (Caucasoid).

One subject required the dosage of concomitant medication (acetaminophen) during the course of the study because of adverse event. Six female subjects used a systemic hormonal contraception during the study.

Protocol deviations documented during the study are presented. The most frequent deviation was that in sampling time; deviations greater than 2 minutes were adjusted to reflect actual sampling time.

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

All subjects were judged eligible for enrolment in this study, based on medical and medication histories, demographic data, vital signs measurements, physical examination, and clinical laboratory tests. The inclusion and exclusion criteria were acceptable.

No clinically significant changes in levetiracetam pharmacokinetics based on sex, race and smoking status has been observed in the literature. The test conditions were sufficiently standardized in order to minimize the variability of all factors involved.

There were several deviations from the protocol, which can be considered as minor with no impact on the study validity. The concomitant medication is considered to have no significant influence on levetiracetam pharmacokinetics.

Analytical methods

The bioanalytical part of the study was done at a Clinical Research Organisation (CRO) in Canada.

Plasma concentrations of levetiracetam were determined using HPLC/MS/MS method.

The validation is declared to be performed on three HPLC systems (LC/MS/MS02, LC/MS/MS03, LC/MS/MS05). Zidovudine was used as the internal standard (IS).

Linearity was demonstrated within the calibration range as well as accuracy and precision.

Acceptable performance was shown at the limit of quantification.

Six batches of human plasma were used to prove acceptable matrix effect.

Dilution integrity was demonstrated for a dilution factor of 5 (with blank plasma).

Stability in plasma was shown for three freeze-thaw cycles as well as for 18.4 hour on bench-top (22 ºC), and long-term stability in plasma at -20ºC was shown for 92 days.

Statement of compliance with GLP, protocol and SOP is presented.

From expected 1280 samples (excluding replicates), 1278 were received (2 samples were missed blood draw). Samples from 4 alternates (160 samples) were not subject to analysis as predefined in the protocol. Therefore, 1118 samples were analyzed.

Plasma concentrations of levetiracetam were determined by the above mentioned validated method in four HPLC systems (LC/MS/MS01, LC/MS/MS09, LC/MS/MS11, LC/MS/MS12).

A total of sixteen calibration curves for acceptable calibration curves were presented. The correlation coefficients were ≥0.9902. Between batch precision and accuracy of the calibration standards ranged from 2.8 % to 4.9% and 96.7% to 103.5%, respectively. The calibration range was from 0.250 to 50.000 mcg/ml of levetiracetam.

Back-calculated mean accuracy and precision of QC samples from all accepted analytical batches in the study ranged between 102.6% to 105.1% and 8.6% to 9.3%, respectively.

Ten samples were reanalysed out of the 1118 analysed study samples (0.9%). Four samples were above upper limit of quantification, six samples lost in processing. No sample was repeated because of pharmacokinetic reason.

The maximum sample storage period was of 31 days.

The CHMP considers that the analytical method has been adequately described and validated, and satisfactory method performance during study sample analysis was demonstrated. The analytical method is considered acceptable Long term stability data in human plasma covers maximum storage period of samples. LOQ 0.250 mcg/ml represents approximately 0.83% of Cmax values, this is considered adequate.

Pharmacokinetic Variables

The following pharmacokinetic parameters were observed or calculated for levetiracetam: AUCt, AUC_{∞}, Cmax, $AUCt/_{\infty}$, Tmax, Kel, and T½.

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

The CHMP considers that the pharmacokinetic parameters calculated are justified,

Statistical methods

Based on published data, the intra-subject coefficients of variation of about 21% and 10% were considered for Cmax and AUC, respectively. Thus, with these expected coefficients of variation and an expected ratio of AUC and Cmax within 92.5% and 107.5%, the study should have a power of at least 80% to show bioequivalence with 27 subjects. In order to account for possible dropouts, 28+4 subjects were included in the study.

Statistical and pharmacokinetic analyses are declared to be generated using Kinetic, an application developed at Algorithme Pharma and SAS (version 9.1.3 or higher) using ProcMix.

ANOVA was carried out on ln-transformed AUCt, AUC_{∞}, C_{max} values and non transformed Kel, and T½ values. The treatment, sequence and period were included in the model as fixed effect; a random factor was also added for the subject effect (nested in sequence).

Non parametric test was performed on Tmax.

Criteria for conclusion of bioequivalence:

As declared in the protocol, for claiming bioequivalence, the 90% geometric confidence intervals of the ratio (T/R) of least-squares means from the ANOVA of ln-transformed AUCt, AUC_{∞} and Cmax should fall within 80%-125% limits.

The CHMP finds the statistical methods appropriate for a single dose study. Standard bioequivalence criteria are proposed for AUC_{0-t} and C_{max}.

Results

Twenty-eight (28) subjects were included in the final statistical data set, four (4) alternates has not been analysed and included, in accordance with the protocol.

Levetiracetam pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h	$T_{1/2}$ h
Test	260.668	270.377	31.147	1.00	7.25
Reference	263.552	272.936	31.301	0.92	7.18
*Ratio (90% CI)	98.67	98.90	100.14		
CV (%)	6.59	6.25	17.59		

$AUC_{0-\infty}$ 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

Safety data

No deaths or serious adverse event was reported during this study.

There were sixty (60) adverse events considered as mild or moderate reported by twenty-four (24) of the thirty-two (32) subjects who received at least one dose of the study medication (safety population).

Eighteen (18) subjects who received test preparation reported thirty-four (24) adverse events. Fourteen (14) subjects who received reference preparation and reported twenty-six (26) adverse events with the reference product.

The most commonly reported adverse events were somnolence, dizziness, headache and nausea.

Conclusions

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

The results of study LVA-P5-042 with 1000 mg formulation CAN be extrapolated to the lower strengths 750 mg, 500 mg and 250 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6

2.4.3 Pharmacodynamics

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

2.4.4 Additional data

Not applicable.

2.4.5 Post marketing experience

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

2.4.6 Discussion on Clinical aspects

The results of one bioequivalence study have been presented. The study was a single centre, randomised, single dose, laboratory-blinded, two-period, two-treatment, two-sequence, crossover trial, performed under fasting conditions in healthy volunteers (males and females).

Each subject received a single dose of respective formulation in each period with 240 ml of water after an overnight fast. Each treatment was administered once according to a randomisation list. Standardised meals were served during each study phase.

The minimum wash-out period was 7 days.

The ratios and 90% CI of AUCt, AUC_{∞}, Cmax ln-transformed values are within the limits of 80-125% as predefined, moreover, they are inside narrower limits of 90 - 111%.

Based on the presented bioequivalence study Matever 1000 mg film coated tablet is considered bioequivalent with the reference product Keppra 1000 mg film coated tablet.

The CHMP considered that as Matever 100mg/ml concentrate for solution for infusion (500mg/5ml) is similar to Keppra 100mg/ml concentrate for solution for infusion (500mg/5ml) with regard to content of active substance and excipients, a formal bioequivalence study is not necessary, in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

2.4.7 Conclusions on clinical aspects

Based on the presented bioequivalence study the CHMP considers that Matever 1000 mg film coated tablet is bioequivalent with Keppra 1000 mg film coated tablet.

The results of study LVA-P5-042 with 1000 mg formulation can be extrapolated to the lower strengths 750 mg, 500 mg and 250 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

The CHMP considered that as Matever 100mg/ml concentrate for solution for infusion (500mg/5ml) is similar to Keppra 100mg/ml concentrate for solution for infusion (500mg/5ml) with regard to content of active substance and excipients, a formal bioequivalence study is not necessary, in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

2.5 Pharmacovigilance

PSUR

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

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

Description of the Pharmacovigilance system

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

Risk Management Plan

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

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

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

2.6 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3 Benefit-Risk Balance

This application concerns a generic version of levetiracetam tablets and concentrate for solution for infusion.

The reference product Keppra is indicated is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy 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.
- 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 levetiracetam was presented. This was considered sufficient by the CHMP. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

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

The test formulation of Matever met the protocol-defined criteria for bioequivalence when compared with the Keppra. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},,

$AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

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

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

4 Recommendation

Outcome

Based on the CHMP review of data on quality, safety and efficacy the CHMP considers by consensus that the risk-benefit balance of Matever as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy; as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy, in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy and in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy, 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

Risk management system and PSUR cycle

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.

The PSUR cycle for the product will follow the PSUR schedule for the reference product.

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

Not applicable.