London, 22 September 2011

EMA/884675/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Levetiracetam Actavis Group

International nonproprietary name: Levetiracetam

Procedure No. EMEA/H/C/2305

Note

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

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List of Abbreviations

alu – aluminium

ANOVA- Analysis of variance

ASMF – Active Substance Master File

AUC0-t - area under the plasma concentration versus time curve from time zero to the last measurable concentration

AUC0-∞ - area under the plasma concentration versus time curve extrapolated to infinity

BE – Bioequivalence

BMI - Body Mass Index

CHMP - Committee for Medicinal Products for Human Use

CI- Confidence interval

Cmax - Maximum measured plasma concentration

13C-NMR – Carbon-13 Nuclear Magnetic Resonance

EEA - European Economic Area

EMA – European Medicines Agency

EPAR – European Public Assessment Report

ERA - Environmental Risk Assessment

EU - European Union

EWP - Efficacy Working Party

FT-IR – Fourier Transform Infra-Red

GC – Gas Chromatography

GCP – Good Clinical Practice

GMP - Good Manufacturing Practice

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

HDPE – High Density Polyethylene

HPLC – High Performance Liquid Chromatography

ICH – International Conference on Harmonisation

INN - International Nonproprietary Name

IPC - In-process Control

K_{el} - Elimination rate constant

LC-MS - Liquid Chromatography- Mass Spectroscopy

LDPE – Low Density Polyethylene

LOD - Limit of detection

LOQ - Limit of quantitation

MAH – Marketing Authorisation Holder

mg – milligram

ml - mililitre

MS – Mass Spectroscopy

N - number (of objects)

Ph Eur - European Pharmacopoeia

PK - Pharmacokinetics

pKa – Acid dissociation constant (also acidity constant)

PSUR – Periodic Safety Update Report

PVC - Polyvinyl chloride

QWP - Quality Working Party

q.s. - Quantum sufficit (as much as suffices)

RH – Relative Humidity

RMP – Risk Management Plan

SD - Standard deviation

SmPC – Summary of Product Characteristics

t1/2 - elimination or terminal half-life

Tmax - time of maximum measured plasma concentration

T/R ratio – Test product /Reference product ratio

TSE/BSE *Transmissible spongiform encephalopathy* /Bovine *spongiform encephalopathy*

UV – Ultraviolet

XRD – X-ray diffraction

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 24 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam Actavis Group, 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 24 June 2010.

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

The applicant applied for the following indication:

Levetiracetam Actavis Groupis indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam Actavis Groupis indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

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

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Keppra 250, 500, 750, 1000 mg Film-coated tablets
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 29/09/2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/00/146/001-026, EU/1/00/146/028-029

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

- Product name, strength, pharmaceutical form: Keppra 100 mg/ml oral solution
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 3 March 2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/00/146/027

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: Alar Irs

- The application was received by the EMA on 24 November 2010.
- The procedure started on 15 December 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 March 2011.
- During the meeting 11-14 April 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 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2011.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 July 2011.
- During the CHMP meeting from 18-21 July 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2011.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 5 September 2011 (updated 16 September 2011).
- During the meeting from 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Levetiracetam Actavis Group on 22 September 2011.

2 Scientific discussion

2.1 Introduction

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

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

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

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

According to the legislation the applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic of a reference product, which is authorised for 6/10 years in a EU member state or in the Community. As the Levetiracetam Actavis Group 100 mg/ml oral solution is similar to the Keppra 100 mg/ml oral solution with regard to content of active substance and excipients, a bioequivalence study is not necessary, according to "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98). The application contains adequate non-clinical and clinical data and the waiver of bioequivalence study has been justified.

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

Levetiracetam Actavis Groupis indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam Actavis Groupis indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Levetiracetam Actavis Group oral solution is presented in 300 ml amber glass bottle with 10 ml graduated oral syringe, 300 ml amber glass bottle with 3 ml graduated oral syringe and an adaptor for the syringe and in 300 ml amber glass bottle with 1 ml graduated oral syringe and an adaptor for the syringe. The latter is different from the reference product which uses a 150 ml bottle but otherwise the proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2 Quality aspects

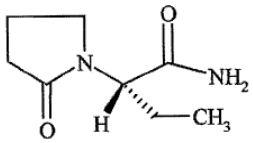
2.2.1 Introduction

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

The product is supplied as an oral solution containing 100 mg/ml levetiracetam. The product will be marketed in 300 ml glass bottles with 3 types of graduated oral syringe. For a full list of excipients refer to the SmPC.

2.2.2 Active Substance

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



A monograph for Levetiracetam is included in the European Pharmacopoeia that came into force since 01.01.2011.
Levetiracetam appears as a white to off-white non-hygroscopic powder, very soluble in water and soluble in methanol and in ethanol.
Levetiracetam has one chiral center, hence exhibits stereoisomerism and exists in two isomers i.e. R & S isomers. The manufacturing process of Levetiracetam followed the proposed active substance manufacturer produces consistently S-isomer. R-Isomer is being controlled to a limit by a validated method.
Levetiracetam produced by the proposed active substance supplier is of crystalline form. The consistency of the form has been established by XRD on three consecutive batches.

Manufacture

The documentation on the active substance is presented using an Active Substance Master File (ASMF) procedure. The synthesis is described in sufficient detail. Critical steps and intermediates are presented in a satisfactory manner. Information regarding process validation has also been presented and is considered acceptable. Results were also presented to show that potentially genotoxic impurities or impurities originating from the starting materials do not carry over to the final active substance.

Specification

Levetiracetam is described in the last edition of the European Pharmacopoeia (Ph. Eur.). The Ph. Eur. monograph specifications have been implemented by the finished product manufacturer, where applicable, to control of the active substance. The specification includes tests and limits for appearance (visual), solubility, appearance of solution (Ph.Eur.), identification (Ph. Eur., HPLC), enantiomeric

purity (Ph.Eur.), specific optical rotation (Ph. Eur.), assay (Ph. Eur.), related substances (HPLC), sulphated ash (Ph.Eur.), heavy metals (Ph. Eur.), water content (Karl-Fischer), residual solvents (GC). Particle size is not considered to be a critical parameter for the active substance used in oral solution. Microbiological purity test is also of no special concern with the chemically synthesised active substance that is used in this liquid oral dosage form that contains antimicrobial preservatives. Hence the omission of testing particle size and microbiological purity from the active substance specifications are considered acceptable.
In-house analytical procedures have been described and validated. Impurities have been evaluated and found to be acceptable from the safety viewpoint.
The certificates of analysis of three/five commercial scale batches manufactured by the active substance manufacturer were enclosed to the Open Part of ASMF. All the results were well within the in-house and Ph. Eur. limits.

Stability

A large number of pilot and commercial scale batches have been studied under long-term (25 °C ± 2 °C, 60 ± 5% RH) and accelerated conditions (40 °C ± 2 °C, 75 ± 5% RH).
The results of six months accelerated stability data shows that there is no significant change in any of the parameters studied in any of these batches.
The results of up to 36 months long-term stability data shows that there is no significant change in any of the parameters studied in any of these batches.
No trends were observed in any of the four batches for the tested parameters either under the long-term or accelerated conditions.
Forced degradation studies are performed and the methods are found to be stability indicating. The active substance undergoes significant degradation when exposed to the stress of oxidative conditions, acid and base treatment. When exposed to water hydrolysis some degradation was observed. No degradation occurred when the drug substance was kept under the high temperature and UV irradiation at 254 nm conditions.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The aim of the development was the formulation of a levetiracetam 100 mg/ml oral solution comparable to the reference product Keppra, 100 mg/ml oral solution.
The excipients chosen for the drug product are mainly based on evaluation of reference product composition and their quantity is within the common range observed for these formulations.
All the excipients comply with the Ph. Eur., except for the Grape flavouring and Ammonium Glycyrrhizate Solution which comply with in-house specifications from the suppliers.
Several formulations were prepared in order to optimize the pH, density and the taste of the drug product. A target pH and density similar to the references product were chosen.
During the development the test for Uniformity of Mass of delivered Doses from Multidose Containers (Ph.Eur. 2.9.27) was carried out on oral syringes.
The preservative efficacy has been tested in accordance with the EU-guideline: Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product, CHMP/QWP/396951/06 and compliance with the Ph.Eur. test for preservative efficacy was demonstrated. The preservative efficacy has been demonstrated at the lower maximum concentration level for the current product.

The assay of levetiracetam, methylparahydroxybenzoate and propylparahydroxybenzoate, pH and density have been analysed before and after the filtration. No trends or out of specification results are observed.

Adventitious agents

Levetiracetam Actavis Group 100 mg/ml oral solution does not contain any materials of human or animal origin.

Manufacture of the product

The manufacturing process is carried out in six steps including information about mixing and stirring times and temperatures, where necessary. Storage time for bulk solution is defined based on available stability data for bulk solution. The filter compatibility has been evaluated on the bulk product batches Reprocessing policy is defined and is in accordance with GMP. The in-process parameters controlled during the manufacture were presented. The process validation has been preformed on three consecutive pilot/production scale batches. The information and results presented in this regard are considered sufficient to ensure the robustness of the process.

Product Specification

The release and shelf-life specification have been presented for the finished product and include tests and limits for: appearance (visual inspection), clarity and colour of solution (Ph. Eur.), identification (HPLC, UV), pH (Ph. Eur.), density (Ph. Eur.), assay (levetiracetam, methylparaben and proplparaben HPLC), related substances (HPLC), microbial test (Ph. Eur.). Analytical procedures are described and validated.
The batch analysis results are available for three pilot batches manufactured by the proposed manufacturer using the drug substance from the proposed supplier. All the results comply with the predetermined criteria.

Stability of the product

Three pilot batches stored at long term conditions (25°C ± 2°C/60 ± 5% RH), intermediate (30°C ± 2°C /65 ± 5% RH) and accelerated conditions (40°C ± 2°C/75 ± 5%RH). Stability study results have been provided for up to 17 months stored at long term and intermediate conditions and for six months in accelerated conditions. All the tested parameters comply with the proposed specifications and there are no changes or trends observed at any of the tested parameters at the long term or at intermediate conditions.
It is confirmed that the first three commercial batches will be added to the stability program. Thereafter, a minimum of one batch annually will be placed on stability in accordance with GMP.

In-use stability
In use stability studies have been performed on one batch stored under the long-term ICH storage conditions at 25°C/60%RH. The results are presented up to 120 days.
All results are in compliance with the specification requirements. The proposed in use stability shelf life is agreed.

Forced degradation study

Forced degradation study has been performed. Samples were stressed under acidic, basic, oxidative, photolytic and thermal conditions. Levetiracetam in drug product is stable in photolytic and thermal stress condition.
The product was found stable at all the conditions but less under acidic and basic conditions.
Both parabens were stable under photolytic conditions. Degradation to the higher extent was observed at basic and at thermal conditions. At acidic and oxidative conditions some small decrease in assay was seen. It can be concluded the product does not show any sensitivity to light.

Based on the overall submitted data the proposed shelf life and storage conditions as defined in the SmPC are justified.

2.2.4 Discussion on chemical, and pharmaceutical aspects

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

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3 Non- Clinical aspects

2.3.1 Introduction

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

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

2.3.2 Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Levetiracetam Actavis Group is considered unlikely to result in any significant increase in the combined sales volumes for all levetiracetam containing products and the exposure of the environment to the active substance. Thus, the Environmental Risk is expected to be similar and not increased. The CHMP agreed with this justification.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for oral solution containing levetiracetam. 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 the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 is of particular relevance.

GCP

Not applicable

Exemption

In accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1., bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution.

In the composition of Levetiracetam Actavis Group the same excipient are used as in the reference product. The comparison of the respective compositions is provided below:

Keppra	**Levetiracetam Actavis Group**
Sodium citrate	Sodium citrate
Citric acid monohydrate	Citric acid monohydrate
Methylparaben	Methylparaben
Propylparaben	Propylparaben
Maltitol liquid	Maltitol liquid
Glycerol	Glycerol
Ammonium glycyrrhizate	Ammonium glycyrrhizate solution
Acesulfame potassium	Acesulfame potassium
Grape Flavour	Grape Flavour
Purified water	Purified water

The CHMP considered that requirements for a bioequivalence study waiver are met.

Clinical studies

Not applicable

2.4.2 Post marketing experience

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

2.4.3 Discussion and conclusion on clinical aspects

The CHMP considered that as Levetiracetam Actavis Group 100 mg/ml oral solution is similar to Keppra 100 mg/ml oral solution with regard to content of active substance and excipients, a bioequivalence study is not necessary, in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The CHMP did not require the applicant to submit a risk management plan because the application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

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.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

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

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a yearly cycle. The next data lock point for the reference medicinal product is 30 November 2011.

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 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 non-clinical studies have been provided for this generic application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics or 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.

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

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

4 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Levetiracetam Actavis Group 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 *adjunctive therapy:*

- *in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.*
- *in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.*
- *in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy*"

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

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

Risk Management System

Not applicable.

PSUR cycle

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

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

Not applicable.

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

Not applicable.