CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levetiracetam Aurobindo 100 mg/ ml, oral solution
Aurobindo Pharma B.V., the Netherlands

levetiracetam

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2179/001/DC
Registration number in the Netherlands: RVG 108795

20 April 2012

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX14
Route of administration:	oral
Therapeutic indication:	as monotherapy in 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 partial onset seizures with or without secondary generalisation in patients > 1 month of age with epilepsy; as adjunctive therapy in myoclonic seizures in patients > 12 years with Juvenile Myoclonic Epilepsy; as adjunctive therapy in primary generalised tonic-clonic seizures in patients > 12 years with Idiopathic Generalised Epilepsy.
Prescription status:	prescription only
Date of first authorisation in NL:	11 November 2011
Concerned Member States:	Decentralised procedure with DE, ES, FR, UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Levetiracetam Aurobindo 100 mg/ml, oral solution from Aurobindo Pharma B.V. The date of authorisation was on 11 November 2011 in the Netherlands.

The product 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.

The product 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.

A comprehensive description of the indications and posology is given in the SPC.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.
The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra. Keppra 250, 500, 750 and 1000 mg film-coated tablets have been registered in the EEA by UCB Pharma through centralised procedure EU/1/00/146/001-029 since 29 September 2000 (original product). For the 100 mg/ml oral solution reference is made to Keppra 100 mg/ml oral solution, which as been registered in the EEA by UCB Pharma, Belgium through centralised procedure EU/1/00/146/027 since 3 March 2003.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.
The MAH provided sufficient justification for not including a bioequivalence study, see section II.3 "Clinical Aspects". This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Levetiracetam is a white or almost white powder, which is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. There is no evidence of polymorphic forms of levetiracetam.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
Ph. Eur. specifications are applied plus additional requirements as per CEP. The drug substance specifications for levetiracetam are considered acceptable. The drug product manufacturer does not have any additional tests included in the drug substance specification. Batch analysis data have been provided.

Stability of drug substance
The retest period for the active substance is 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Levetiracetam Aurobindo 100 mg/ml is a clear, colourless, grape flavoured liquid.

The excipients are:
- maltitol liquid (E965), glycerol (E422), propylene glycol, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), citric acid monohydrate (E330), sodium citrate, acesulfame potassium (E950), purified water
- Mafco Magnasweet containing glycerine, monoammonium glycyrrhizinate.
- Grape Flavour containing flavourings, propylene glycol, ascorbic acid.

The oral solution is packed in 150 ml or 300 ml amber glass bottles (type III) with a white child resistant closure (polypropylene). The bottles are packed in a cardboard box containing a 1 or 3 ml oral syringe graduated respectively every 0.05 ml (corresponding to 5 mg) and every 0.1 ml (corresponding to 10 mg) (in the 150 ml pack), or a 10 ml oral syringe graduated every 0.25 ml (corresponding to 25 mg) (in the 300

ml pack). The oral syringes are made of polypropylene and an adaptor for the syringe is included. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and the functions explained. It was aimed to develop a product equivalent to the reference product Keppra 100 mg/ml oral solution. The amounts of maltitol, methyl parahydroxybenzoate, and propyl parahydroxybenzoate are the same as for the innovator product. The formulation does not contain any excipient which may affect the gastrointestinal transit or absorption of the active substance. No overages of drug substance are included in the formulation.

No bioequivalence studies have been performed; adequate justification is provided from a chemical-pharmaceutical point of view. The choices of the packaging and manufacturing process are justified. Suitability of the preservative was shown.

Microbiological attributes

Methyl parahydroxybenzoate and propyl parahydroxybenzoate are added as a preservative to prevent proliferation or to limit microbial contamination, which could occur during normal conditions of storage and use, particularly for multidose container. The effectiveness of the preservative has been shown. Limits are set to ensure the consistency of the preservative effect during storage.

Manufacturing process

The manufacturing process concerns a 4 stage process with 13 steps, including preparation of the bulk solution, final volume make up, filtration, filling and capping. The product is manufactured using a straight-forward (standard) process; validation on pilot-scale batches is therefore acceptable. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

All excipients comply with their specifications of the Ph.Eur. monographs. Except for the sweetener Mafco Magnasweet and grape flavour, for which in-house specifications have been set. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, pH, assay, content of preservative, relates substances, uniformity of weight (mass) of delivered doses, microbial contamination, deliverable volume and weight per ml. The release and end-of-shelf-life specification are identical, except for content of preservative and related substances. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two batches of the smallest size, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for two batches of the smallest batch size (in 300 ml bottles) stored at 25°C/60%RH (12 months), and 40°C/75%RH (6 months). In-use stability was studied on these batches as well, for which 7 months data are available. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Amber colored glass bottles, made of Type-III (*i.e.* soda-lime) glass, closed with white opaque pilferproof child resistant closure made of polypropylene with expanded polyethylene wad. Photostability studies were conducted in line with the ICH guidelines. Results showed no degradation under the influence of light.

The proposed shelf-life of 24 months is justified. The product does not required any special storage conditions. The acceptable in use storage is 7 months.

Several commitments have been made with regard to the finished product; these can be found on page 7 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Keppra, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of levetiracetam released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Levetiracetam is a well-known active substance with established efficacy and tolerability.

The absence of a bioequivalence study has been adequately justified in accordance with Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98. According to this guideline 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. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.) or absorption the same requirements for similarity in excipients apply for oral solutions as required for biowaivers of immediate release dosage forms.

The qualitative composition of the generic levetiracetam oral solution can be considered as similar to that of Keppra oral solution. The only differences are:

- additional sweetener in the generic formulation, i.e. Mafco Magnasweet
- additional taste masking agent, i.e. ammonium glycyffhizate in the innovator's formulation which is not present in the generic product.

The above mentioned differences in the qualitative composition are not expected to affect bioavailability of levetiracetam, which is a highly soluble and permeable drug. Moreover, the amount of the excipient maltitol (that might affect the absorption of an active substance) used in the generic levetiracetam oral solution, is similar to that in Keppra oral solution, i.e. 290 vs 300 mg/ml. Therefore, it is acceptable to waive a BE study for Levetiracetam Aurobindo 100 mg/ml, oral solution.

Pharmacovigilance
The innovator product Keppra currently has a one-year PSUR cycle. Therefore, the MAH agreed to follow a one-year PSUR cycle upon approval for Levetiracetam Aurobindo. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old, which is in correspondence with the agreed PSUR cycle of the innovator product.

The MAH committed to continue to monitor the following events: abnormal behaviour, blood dyscrasias, seizure worsening, long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children and safety in patients with different epilepsy syndromes younger than 12 months. In addition, the impact of levetiracetam on the teeth in children of this age group should be carefully monitored in post marketing.

Risk management plan
Levetiracetam was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levetiracetam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their

disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in line with the SPC for the innovator product.

Readability test
The package leaflet has not been evaluated via a user consultation study. A bridging statement has been submitted with reference to the succesful user test on the PL of another product. Besides, the leaflet is similar to the PL of Keppra which has been succesfully user tested.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levetiracetam Aurobindo 100 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Keppra 100 mg/ml oral solution. Keppra is a well-known medicinal product with an established favourable efficacy and safety profile.

The absence of a bioequivalence study has been adequately justified and was accepted. In conclusion, the qualitative composition is considered similar to that of Keppra oral solution. The differences in taste masking agents and sweetener are not expected to affect bioavailability of levetiracetam, which is a highly soluble and permeable drug.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levetiracetam Aurobindo 100 mg/ml, oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 October 2011. Levetiracetam Aurobindo 100 mg/ml, oral solution was authorised in the Netherlands on 11 November 2011.

Six-monthly specific safety reports for children < 4 years old should be submitted conform the data lock point for the innovator product.

The date for the first renewal will be: 31 July 2016.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to demonstrate the efficacy of anti-microbial preservation at the end of shelf life for the submission batches placed on stability.
- Two batches of the smallest batch size of the bulk solution are subjected to validation. Commitments are made to perform validation on the remaining third batch and the batches of intermediate and large size.
- The MAH committed to perform validation on a third batch.
- The MAH committed to continue the ongoing long-term stability studies of the submission batches of finished product as per the study design presented.
- The MAH committed to carry out accelerated stability studies (at 40°C/ 75%RH) and long-term stability studies (at 25ºC/60%RH) on the first production batch packed in the 300ml bottle pack and on the first three production batches packed in the 150 ml bottle pack.
- The MAH committed to place one batch on stability under long term storage conditions annually.
- The MAH committed to perform in-use stability studies at the end of shelf-life.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached