CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levetiracetam 100 mg/ml Teva, concentrate for solution for infusion Teva Nederland 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/2194/001/DC
Registration number in the Netherlands: RVG 108443

22 March 2012

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX14
Route of administration:	intravenous
Therapeutic indication:	as monotherapy 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 adults and children > 4 years 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 authorisation in NL:	29 December 2011
Concerned Member States:	Decentralised procedure with BE, DE, FR, IT, LU
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 100 mg/ml Teva, concentrate for solution for infusion from Teva Nederland B.V. The date of authorisation was on 29 December 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 and children from 4 years 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 Teva concentrate is an alternative for patients when oral administration is temporarily not feasible.

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, which was first registered in the EEA on 29 September 2000 by UCB Pharma through centralised procedure EU/1/00/146/001-029 (original product). This first authorisation concerned film-coated tablets. Keppra 100 mg/ml concentrate for solution for infusion was approved in the EEA on 29 March 2006.

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. As Levetiracetam 100 mg/ml Teva is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current 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 to off-white powder, which is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. Levetiracetam has one chiral center and the S-enantiomer is produced. The polymorphic form of the drug substance has been identified and is consistently produced and stable.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The information on the manufacturing process is acceptable, with appropriate data on the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is determined in-house. The Ph.Eur. monograph of levetiracetam is implemented. The limits are in line with or more stringent than those described in the monograph. The limits for residual solvents are in line with the ICH guidance and the microbial limits are in line with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for four batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months). The stability results show no significant changes or trends under long-term or accelerated storage conditions. In view of the provided stability data, the proposed re-test period of 36 months is justified. The drug substance does not require specific storage conditions. The photostability of the drug substance has been demonstrated in line with ICH Q1B.

** 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 100 mg/ml Teva is a clear, colourless concentrate with pH 5.0-6.0 and osmolarity of 300-370 mOsm/kg.

The concentrate for solution for infusion is packed in 5 ml glass vials (type I) with a Teflon coated bromobutyl rubber stopper and sealed with an aluminium/polypropylene flip off cap. Each 5 ml vial contains 500 mg of levetiracetam.

The excipients are: sodium acetate trihydrate, sodium chloride, glacial acetic acid, water for injection.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation is based on and is comparable with the originator's finished product, Keppra by UCB Pharmaceuticals Inc. The formulation and process were optimized on pH, sequence of addition, nitrogen purging and filter adsorption.
A manufacturing overage of 10 to 12% is proposed for the full-scale process, depending on the exact scale. This is justified based on the applied overfill (fill volume 5.2-5.4mL), loss due to monitoring of in-process controls and loss during manufacturing. The MAH committed to validate the loss during filtration by analysis of the values of commercial manufacturing.
The final formulation has the same qualitative composition as the innovator product. The omission of a bioequivalence study is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the dissolution of the ingredients in water for injection, sterile filtration of the bulk solution, filling of the solution in vials and terminal sterilization. The description of the manufacturing process is acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. Validation on full-scale batches will be done post-approval. The MAH committed to provide the maximum manufacturing time for which compliance with the limit for one impurity has been validated.

Container closure system
For all packaging materials, specifications, certificates of analysis and technical drawings have been provided. The glass bottles and the rubber closures comply with Ph.Eur. monographs 3.2.1 and 3.2.9, respectively.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological attributes
The sterility of the product is tested on a routine basis at release and shelf life to ensure the integrity of the product, according to Ph.Eur. method 2.6.1. The bacterial endotoxins of the product are tested on a routine basis at release and shelf life to ensure the integrity of the product, according to the Ph.Eur. method 2.6.14. This is acceptable.

Quality control of drug product
The specification is deemed acceptable and includes tests for appearance, identification, pH, particulate contamination, extractable volume, assay, related substances, R-isomer, sterility and bacterial endotoxins. The release and shelf-life specification differ in the absence of tests on identification and impurities in the shelf-life specification. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored in market pack at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. It has been demonstrated that the final drug product is photostable.
The products demonstrate an increase in impurities and assay. No changes in any of the other parameters were observed. These results remain within limits and no differences are observed between the upright and inverted stored batches. Based on the results, a shelf life of 24 months was granted without specific storage conditions.

Compatibility of the drug product with sodium chloride 0.9%, Ringers lactate solution and dextrose 5% has been tested for 24 hours at 25°C/60%RH in PVC infusion bags. This is acceptable as no other diluents or containers are stated in the SPCs of the proposed drug product and the innovator. In-use stability data demonstrate compatibility with the diluents described in the SPC for 24 hours in PVC infusion bags.

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.

Levetiracetam 100 mg/ml Teva is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Levetiracetam 100 mg/ml Teva concentrate for solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 leaflet user test scored 100% for locating the information necessary to answer the questions and 100% for understanding of this information. The leaflet user test passed the defined success criteria: 90% of the test participants are able to find the information requested within the package leaflet of which 90% can show that they understand it. Therefore the test is considered approvable.

It is noted that the product information should be in line with that of the innovator. This product information has already been tested.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 100 mg/ml Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 September 2011. Levetiracetam 100 mg/ml Teva, concentrate for solution for infusion was authorised in the Netherlands on 29 December 2011.

The date for the first renewal will be: 12 September 2016.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to validate the loss during filtration by analysis of the values of commercial manufacturing.

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