Decentralised Procedure

Public Assessment Report

Levetiracetam Desitin 250/500/750/1000 mg befilmtes Granulat im Beutel

Levetiracetam

DE/H/2986/H/001-004/DC

Applicant: Desitin Arzneimittel GmbH

| Reference Member State | DE |
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<td>INN (or common name) of the active substance(s):</td>
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<td>Coated granules in sachet; 250/500/750/1000 mg</td>
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<td>Reference Member State:</td>
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<td>Member States concerned:</td>
<td>CZ, ES, PT, RO, SK, UK</td>
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<td>Applicant (name and address)</td>
<td>Desitin Arzneimittel GmbH</td>
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<td>Weg beim Jäger 214, 22335 Hamburg, Germany</td>
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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for “Levetiracetam Desitin 250/500/750/1000 mg coated granules in sachet”,

- 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 and children with a body weight of at least 25 kg 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 approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised procedure concerns a novel formulation of levetiracetam, under the trade names “Levetiracetam Desitin 250/500/750/1000 mg coated granules in sachet”. In this Assessment Report, the name “levetiracetam” is used. The product was formerly named “Desitin Levetiracetam 250/500/750/1000 mg coated granules in sachet”, which has meanwhile been changed.

The originator product is “Keppra 250/500/750/1000 mg film-coated tablets” by UCB Pharma SA, registered across the EU via centralised procedure since 29th September 2000. Apart from the tablet formulation, “Keppra” is available as oral solution (100 mg/ml) since 3rd March 2003 and as concentrate to prepare a solution for infusion (drip into a vein, 100 mg/ml) since 29th March 2006. For the novel coated granule formulation, the applicant therefore pursues an application according to Art. 10(3) of Dir. 2001/83/EC as amended.

With Germany as the Reference Member State in this Decentralised Procedure, Desitin Arzneimittel GmbH is applying for the Marketing Authorisations for “Levetiracetam Desitin 250/500/750/1000 mg coated granules in sachet” in Czech Republic, Spain, Portugal, Romania, Slovakia, and The United Kingdom.

II.2 About the product

Levetiracetam (LEV) is classified in the ATC-code N03AX14, i.e. the pharmacotherapeutic group “Other antiepileptics”.

It is a broad-spectrum antiepileptic drug (AED) which is effective against a variety of seizure types. LEV is a pyrrolidine derivative with a novel mechanism of action by modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain. The pharmacokinetic advantages of LEV compared to other AEDs include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of drug-drug interactions and partial metabolism outside the liver.

LEV is indicated as monotherapy for the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. In addition, LEV is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from approx. 12 years of age with epilepsy, in the treatment of myoclonic seizures in adults and adolescents with Juvenile Myoclonic Epilepsy (JME) and in the treatment of primary generalised tonic-clonic seizures in adults and adolescents with Idiopathic
Generalised Epilepsy (IGE). The originator Keppra® has been authorized for children from 4 years of age (approved September 2005) and more recently for children from 1 month to 4 years old (approved September 2009). The lowest dose strength of the intended coated granules is 250 mg which is suitable for children weighing at least 25 kg (10 mg/kg twice daily). For this reason the applicant has restricted the applied indication in children to the minimum weight of 25 kg, which is endorsed as the applicant has made a commitment to adapt the wording of the indication to the originator Keppra as soon as he will have obtained approval for a levetiracetam containing oral solution.

II.3 General comments on the submitted dossier
The submitted dossier is of satisfactory quality in line with prevailing European requirements.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The bioequivalence study is stated to be compliant with the relevant guidelines for GCP.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
Levetiracetam is included in the European Pharmacopoeia 7th edition, which is legally valid from 01.01.2011. The active substance Levetiracetam is also described in USP 34. An Active Substance Master File (ASMF) for Levetiracetam from the active substance manufacturer and an amendment is submitted. The chemical-pharmaceutical documentation and Expert Report in relation to R levetiracetam are of sufficient quality in view of the present European regulatory requirements.
The route of synthesis is adequately characterised. The choice of etiracetam as starting material has been adequately justified. The structure of levetiracetam has been confirmed by analytical evidence like elemental analysis, by spectroscopic analyses (IR, 1H-NMR, 13C-NMR, MS and XRD). The control tests and specifications for drug substance are adequately drawn up. The analytical methods have been sufficiently validated.
Sufficient batch analysis data have been presented.

Stability data are presented for three batches each of levetiracetam manufactured by option 1 and option 2 at real time (25° C/60 % RH) up to 48 month (option 1) resp. 12 month (option 2) and accelerated conditions (40° C/75 % RH) for 6 month (only option 1). Batches were packed in containers identical to the market container. Furthermore forced degradation studies with levetiracetam were performed by treatment with heat, under acidic and alkaline conditions, under oxidizing conditions as well as under light stress conditions. The results indicate that the assay and chromatographic purity methods are stability indicating. The Levetiracetam, manufactured by validated manufacturing process is stable up to 48 month at long term and for 6 month at accelerated conditions. No significant changes were observed for any of the tested parameters throughout storage.

Drug Product
The development of the product has been described sufficiently, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis data of the same batches as used for stability testing are provided. The data demonstrate good compliance with the release specification. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. For stability testing of the finished product, a bracketing design is applied as the fill weight of the coated minitablets is the only difference between the dosage strengths of the drug product. Different amounts of the same coated minitablets (bulk) are filled in sachets consisting of the same multi-layer foil (paper/alu/PE) to generate different dosage strengths. The results presented for two production scale batches of 250 mg, 1000 mg and 1500 mg Coated granules in sachet and one batch each for 375 mg, 500 mg, 750 mg, and 1250 mg strength show that all specified parameters are fulfilled under long term (25°C/60 % RH) and intermediate (30°C/65 % RH) up to 18 month and accelerated conditions (40°C/75 % RH) for six month for the coated granules in sachets. Neither specified impurity etiracid nor any unspecified impurity above the corresponding limit of quantitation was found. No tendencies were observed. The data show that the stability profiles among the different strengths are comparable. No storage condition is required.

A shelf-life of 24 months is accepted for Levetiracetam Desitin 250/500/750/1000 mg coated granules in sachet with no specific labelling recommendation.

III.2 Nonclinical aspects

Pharmacology

Levetiracetam is a second generation anticonvulsant that belongs to the class of pyrrolidones. The mechanism of action of levetiracetam has not been completely unravelled yet, but comprises partial inhibition of N-type Ca2+ currents and binding to the synaptic vesicle protein 2A (SV2A) in the CNS, a protein involved in neuronal vesicle fusion and neurotransmitter release. Only the unchanged S-enantiomer exerts pharmacological activity; the R-enantiomer as well as the major and all minor metabolites of levetiracetam are inactive.

Levetiracetam lacks anticonvulsant activity against acute seizures induced by maximal electroshock or pentylenetetrazole, but significantly protects against partial seizures with secondary generalisation in kindling models induced by pilocarpine or kainic acid or effectively prevents generalised tonic-clonic, myoclonic or absence seizures in mice and rats. In SV2A-/- mice, levetiracetam increases the seizure threshold. Levetiracetam also protects against mitochondrial dysfunctions during seizures, increases the production of nitric oxide, provides analgesia in chronic pain models and confers neuroprotection in animal models of stroke, head trauma and subarachnoid haemorrhage.

In safety pharmacological investigations, levetiracetam showed a wide safety margin with regard to adverse CNS effects and exerted no clinically relevant activity on ECG parameters. However, the consequences of decreased serum osteocalcin levels in rats including the potential risk for microstructural changes of bone matrix in response to levetiracetam treatment warrants further elucidation.

Pharmacokinetics

Orally administered levetiracetam is rapidly (tmax < 1 h) and completely absorbed with low interspecies differences in mice, rats, rabbits and dogs. Mean peak plasma concentrations are achieved between 40 min in mice and about 55 min in other species. Plasma half-life is short and amounts to 1.3-1.5 h (mice), 1.8-2 h (rat), 2.3-3.1 h (dog) and 4 h (rabbit), respectively. Levetiracetam does not bind to plasma proteins and reaches higher than blood concentrations in kidney and pituitary gland, whereas lower concentrations are found in the CNS despite effective permeation across the blood-brain-barrier. Levetiracetam is no substrate for human P-glycoprotein, which could explain the prolonged efflux from the brain and long duration of action.

Levetiracetam is primarily hydrolysed to the inactive metabolite 2-pyrrolidine N-butyric acid (PBA). Further metabolites are generated by oxidation at positions 3,4 or 5 of the 2-oxopyrrolidine ring or by oxidation at position 5 and subsequent hydrolysis. Levetiracetam is predominantly eliminated unchanged via urine (> 80 % of the administered dose) across species including humans. The parent drug accounts for ~66 %, the PBA metabolite for ~24 % of the administered dose in human urine.
Consequently, pharmacokinetic interactions of levetiracetam with cytochrome P450 isoforms, UDP-glucuronyltransferases and epoxide hydrolase are considered unlikely.

**Toxicology**

Following oral administration, a reversible increase of liver weight and hypertrophy of centrilobular hepatocytes was found at 300 mg/kg/d in rats and mice. In addition, dose-dependent hyaline droplet nephropathy accompanied by chronic progressive nephropathy was detected in male rats at 200-300 mg/kg/d in gavage and at 50/mg/kg/d in dietary studies. No deaths, organ failure or other irreversible toxicity was seen after long-term oral treatment up to 1800 mg/kg/d in rats, 960 mg/kg/d in mice and 1200 mg/kg/d in dogs.

Levetiracetam was neither mutagenic, nor carcinogenic in mice or rats. In reproduction toxicity studies, no influence on fertility became evident. In female rats, levetiracetam affected the hypothalamic-pituitary-gonadal axis leading to increased ovarian weight and number of corpora lutea, higher testosterone, but reduced estradiol, progesterone and FSH levels. This might be attributed to the interaction of levetiracetam with ovarian SV2A protein. Moreover, decreased foetal weight and minor skeletal abnormalities were observed at 3600 mg/kg/d in pregnant rats corresponding to 12-times the MRHD. Skeletal variations, increased embryo-foetal mortality and resorption rates were also apparent at 600-1800 mg/kg/d in rabbits. In mice, i.p. administration of 2000 mg/kg/d levetiracetam increased resorption rates, while skeletal abnormalities, specifically hypoplastic phalanges, were induced at 1200 mg/kg/d. No effects on pre-/postnatal development until weaning were noted in rats up to 1800 mg/kg/d, which amounts to approximately 6-times the MRHD.

In sum, the pharmacological and toxicological characteristics of levetiracetam are well known and have been appropriately documented based on publicly available information. The impurities contained in drug substance and drug product, respectively, comply with prevailing requirements. The instructions on use of the product during pregnancy and the preclinical safety data delineated in the proposed SmPC and PL, respectively, were completely harmonised with the current texts of the reference product “Keppra” (EMEA/H/C/277/N/118). Moreover, a disposal advice has been added to the SmPC. Marketing authorisation is recommended from a non-clinical point of view.

### III.3 Clinical aspects

**Pharmacokinetics**

This application concerns four strengths (250/500/750/1000 mg) of the active substance levetiracetam. Different amounts of coated granules are packed into sachets to receive the different strengths. The submitted data suggest bioequivalence of ‘Levetiracetam Desitin 1000 mg befilmtes Granulat im Beutel’ with ‘Keppra 1000 mg film-coated tablets’ (and of ‘Levetiracetam Desitin 1500 mg befilmtes Granulat im Beutel’ with 2 tablets of ‘Keppra 750 mg film-coated tablets’, respectively).

In view of the formulation's characteristics of fast immediate release, and in view of the substance's pharmacokinetics with a fast and extensive pharmacokinetic input with nearly complete systemic bioavailability on oral dosing and dose-proportional concentrations resulting from a dose-independent extent of bioavailability, clearance and rate of disposition, the present results of the bioequivalence studies also apply to the other strengths that are subject of the present application since these only differ with regard to the number of film coated granules contained in the unit dose sachet.

**Pharmacodynamics**

Levetiracetam has a different mechanism of action from that of other AEDs. It is not effective in standard animal models used for screening anticonvulsant activity, but is effective in the chronic kindling models. At the molecular level, the most relevant mechanism of action for Levetiracetam is through binding to the synaptic vesicle protein SV2A resulting in a reduction in the rate of vesicle release. Other mechanisms have been identified which include reversal of inhibition of neuronal GABA- and glycine-gated currents by zinc and β-carbolines, and partial depression of the N-calcium current. Currently, a clinical efficacy profile has not been identified for Levetiracetam from its observed mechanisms of action.
Levetiracetam protects against seizures with a focal onset and a seizure phenomenology mimicking human partial seizures in an animal model. In addition, Levetiracetam exhibits potent antiepileptic effect against a variety of seizure types in animal models of chronic and genetic epilepsy. In adult patients with pharmacoresistant focal epilepsies, a correlation between the antiepileptic effects of Levetiracetam and its peak serum concentration was observed.

Levetiracetam exhibits an antiepileptogenic effect in animal models of kindling; however, the mechanism of this effect remains unknown. Levetiracetam was shown to have significant antiepileptic activity in children affected by symptomatic focal epilepsy and pharmacoresistant continuous spikes and waves during slow sleep. No detrimental cognitive effects were observed in adult patients with partial or generalised seizures receiving Levetiracetam.

**Clinical efficacy**
The efficacy of levetiracetam in epilepsy has been well documented in literature. No new efficacy data were submitted. Depending on the indication, the age ranges applied for are either adults from 16 years of age, adolescents or children with a body weight of at least 25 kg with epilepsy. The originator Keppra® has been authorized for children from 4 years of age (approved September 2005) and more recently for children from 1 month to 4 years old (approved September 2009). The lowest dose strength of the intended coated granules is 250 mg which is suitable for children weighing at least 25 kg (10 mg/kg twice daily). For this reason the applicant has restricted the applied indication in children to the minimum weight of 25 kg.

**Clinical safety**
No new data were submitted.

**Assessment of User Testing**
In order to meet the requirements of Directive 2004/27/EC, diagnostic user testing was carried out on the package leaflet for Levetiracetam Desitin 250/375/500/750/1000/1250/1500 mg sachet with coated granules.

The test was performed in London, UK with an English mock-up version of the PIL during 18th July 2010 and 26th July 2010.

The performed user test comprised the following steps:
- A pre-test to detect any major legibility and comprehensibility problems among 4 subjects and two main test rounds among 10 subjects each.
- The developed questionnaire contained 17 questions specific to Levetiracetam Desitin and 3 specific to the format of the package leaflet.
- The questions covered the relevant aspects of drug administration, contra-/ indication, warnings, undesirable effects, pregnancy and ability to drive.

During both main test rounds all subjects were able to find the relevant information to all questions and give correct answers to all questions.

No revisions of the PIL were suggested after any of the test rounds.

The results demonstrate a sufficient percentage of identification and comprehension of product related information. (Date of revision of the test report has been clarified (06.08.2010).
Pharmacovigilance system

Description of Pharmacovigilance System
The applicant has provided documents that set out a detailed description of the Desitin Arzneimittel GmbH system of pharmacovigilance (Version 6 dated 10 May 2010). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published non-clinical and clinical data.

The submitted data suggest bioequivalence of ‘Levetiracetam Desitin 1000 mg befilmtes Granulat im Beutel’ with ‘Keppra 1000 mg film-coated tablets’ (and of ‘Levetiracetam Desitin 1500 mg befilmtes Granulat im Beutel’ with 2 tablets of ‘Keppra 750 mg film-coated tablets’, respectively). The results of studies Nos. LEV-001/K and LEV-002/K, respectively with Levetiracetam Desitin 1000mg and 1500 mg befilmtes Granulat im Beutel can be extrapolated to the other strengths 250/500/750.

SPC and PIL have been amended in line with the originator PI.

The application is approved.