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Committee for Medicinal Products for Human Use (CHMP)

Keppra

(levetiracetam)

Procedure No. EMEA/H/C/0277/P45 FUM052

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AED	Anti Epileptic Drug
BID	Bis In Die (twice a day)
CBZ	Carbamazepine
ICES	International Classification of Epileptic Seizure
ILAE	International League Against Epilepsy
LEV	Levetiracetam
MAH	Marketing Authorization Holder
NOS	Not Otherwise Specified
(S)AE	Serious Adverse Event
SD	Standard Deviation

I. RECOMMENDATION

The MAH has fulfilled its obligations towards article 45 of the of the paediatric regulation EC/1901/2006, and as such this FUM can be considered fulfilled and grantable.

II. INTRODUCTION

Levetiracetam (LEV), a pyrrolidone derivative, is an antiepileptic drug (AED) structurally unrelated to any other known AED. The exact way in which levetiracetam works is still unclear but it seems to interfere with a protein called the synaptic vesicle protein 2A, which is found in the space between nerves (synapses) and stops the release of chemical messengers between nerve cells. This helps to stabilise electrical activity in the brain and prevent seizures.

The product is used to treat partial onset seizures (fits) with or without secondary generalization, or as an adjunctive therapy in patients suffering from:

- partial onset seizures with or without generalisation in patients from four years of age
- myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in patients from 12 years of age with juvenile myoclonic epilepsy
- primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause)

Keppra (levetiracetam) is available in the European Union as 250 mg, 500 mg, 750 mg and 1000 mg tablets, 100 mg/mL oral solution, and 5 mg/5mL concentrate for solution for infusion.µ

III. TYPE OF APPLICATION

In the frame of the article 45 of the paediatric regulation EC/1901/2006, UCB provided in January 2008 a listing with all submitted and not yet submitted paediatric clinical data on the medicinal products registered by UCB or its affiliates in the Union. In December 2008, UCB provided the EMEA with the actual data listed previously as having never been submitted by UCB to the Competent Authority in the frame of a paediatric filing. This assessment concerns the overview of these studies.

IV. SUBMITTED STUDIES

The MAH submitted 8 studies, see table 1, in compliance with the requisite of art. 45. Neither of these studies had investigations in paediatric patients as an objective, but some of the participating subjects were under the age of 18 at time of inclusion. As such they were protocol deviators. In the frame of compliance with art. 45 EC/1901/2006, the MAH only focused on these subjects. The safety data pertaining to those patients have been extracted from the total population, with the aim of investigating if any new safety signal would be observed, that would alter the known benefit/risk in paediatric patients. Since those data only include a few patients per trial under the age of 18 years, The MAH argued that no relevant information on efficacy in children/adolescents can be derived from those reports.

CHMP comment:
Agreed

Table 1: Studies submitted in the framework of compliance with art. 45 EC/1901/2006

A Multicenter, Double-Blind, Follow-Up Trial Evaluating The Longterm Safety Of Levetiracetam (1000 To 3000 Mg/Day B.I.D.) And Carbamazepine (400 To 1200 Mg/Day Oral B.I.D.), Used As Monotherapy In Subjects (16 Years) Coming From The N01061 Trial
A Phase IV - Pharmacovigilance Study Of Keppra(R) Greece - S.K.A.T.E.: Safety Of Keppra(R) As Adjunctive Therapy In Epilepsy
A Korean Open-Label, Multi-Center, Community-Based Trial Assessing The

Efficacy And Safety Of Levetiracetam As Adjunctive Therapy In Adult Subjects With Uncontrolled Partial Epilepsy For Bridging Purpose With A Similar Study On Caucasian Epileptic Subjects
A Double-Blind, Placebo-Controlled, Randomized Study: 16-Week Evaluation Of The Efficacy And Safety Of Levetiracetam (Lev) As Addon Therapy In Adults And Adolescents Older Than 16 Years Suffering From Partial Seizures
K.E.E.P.E.R. (Keppra(R) Epilepsy Evaluation Of Patient Time To Response). A Phase Iv, Open-Label, Multi-Center, Community-Based Trial Studying The Safety And Efficacy Of Levetiracetam As Add-On Therapy In Adult Patients With Treatment-Resistant, Partial-Onset Epilepsy
Anwendung Der In Deutschland Zugelassenen Keppra(R) – Tabletten Als Zusatzbehandlung Bei Erwachsenen Patienten Mit Fokalen Epilepsien
A Phase IV, Open-Label, Multi-Center Community-Based Trial Studying The Safety And Efficacy Of Keppra. As Adjunctive Therapy In Adult Patients With Uncontrolled Partial Epilepsy. S.K.A.T.E.: Safety Of Keppra. As Adjunctive Therapy In Epilepsy
Bridging Study Of L059 (Levetiracetam) In Patients With Epilepsy By Double Blind Method

V. BIOPHARMACEUTICS

There was no new paediatric data to report in any of the above studies.

CHMP comment:
Agreed

VI. PHARMACOLOGY

There was no new paediatric data to report in any of the above studies.

CHMP comment:
Agreed

VII. EFFICACY

Due to the low number of patients below the age of 18 in each trial no relevant information could be gleamed from the reports. The MAH therefore makes reference to the registered data evidencing efficacy in paediatric patients.

CHMP comment:
The MAH's sentiment regarding the fact that due to the low number of paediatric subjects in each study comprehensive paediatric efficacy conclusions could not be drawn is corroborated.

VIII. SAFETY

In order to assess the safety signals in <18y olds, events seen in each of the studies in table 1 will be presented together with a summary of the study's characteristics.

1. A Multicenter, Double-Blind, Follow-Up Trial Evaluating The Longterm Safety Of Levetiracetam (1000 To 3000 Mg/Day B.I.D.) And Carbamazepine (400 To 1200 Mg/Day Oral B.I.D.), Used As Monotherapy In Subjects (16 Years) Coming From The N01061 Trial

This study was a multicenter, double-blind, parallel-group monotherapy long-term follow-up trial. The main objectives were to allow the subjects having benefited from levetiracetam or carbamazepine monotherapy in study N01061 to remain on the same investigational product, to ensure blindness of N01061 treatment identity until N01061 database lock and to continue to assess the safety of LEV as per adverse event reporting.

Subjects included in the trial were to be 16 years or older and newly diagnosed with epilepsy (partial onset seizures with clear focal origin or generalized tonic-clonic seizures without clear focal origin) and had to be previous participants of the double-blind monotherapy study N01061.

In total 335 (of which 171 took levetiracetam) subjects entered the follow-up study. 6 subjects of the LEV and 6 subjects of the CBZ groups were below 18 years of age (mean age equal to 16.9 and 16.6 respectively). Male representation was 66.7% and 16.7% in both groups respectively.

In each group three of the sub-18 subjects reported an adverse event. Two subjects in the LEV group and one in the CBZ group reported a drug-related AE (see table 2). No AEs leading to premature discontinuation or SAEs were reported at all.

Table 2: Drug related AEs reported by <18 year old subjects in both treatment groups

LEV	• One patient each reported: diarrhoea, ligament sprain, weight increased (ADR) • Two patients each reported: upper respiratory tract infection, headache, pharyngolaryngeal pain.
CBZ	• One patient each reported: eye allergy, influenza, hockey injury, lymphocyte count decreased (ADR), headache, acne (ADR)

2. A Phase Iv - Pharmacovigilance Study Of Keppra(R) Greece - S.K.A.T.E.: Safety Of Keppra(R) As Adjunctive Therapy In Epilepsy

This trial was a multi-center, Phase IV pharmacovigilance therapeutic use study. The trial was stopped one year after the recruitment of the first subject. The aim of this trial was to further assess the safety of Keppra, to assess the optimal dose in daily clinical practice and to evaluate the efficacy of Keppra in community-based practice.

Subjects received levetiracetam in a mean daily dose of 1382.1 mg (SD = 257.7 mg) and the median duration of exposure over that period was 99 days.

35 Caucasian subjects entered the study of which one was a female patient aged 17 at the study's start. She received 2000 mg of Keppra per day. She reported a non-serious mood alteration NOS, assessed as unlikely related to study drug, which resolved in 17 days after LEV dose reduction.

3. A Korean Open-Label, Multi-Center, Community-Based Trial Assessing The Efficacy And Safety Of Levetiracetam As Adjunctive Therapy In Adult Subjects With Uncontrolled Partial Epilepsy For Bridging Purpose With A Similar Study On Caucasian Epileptic Subjects

This trial was a multi-center, open-label, add-on study without control group which had as objectives the evaluation of levetiracetam efficacy in community-based epileptic population with partial onset seizures and to obtain further information about optimal dose in daily practice and the further evaluation of the safety and the tolerability of levetiracetam in a broad population of epileptic subjects and confirm the favorable safety of the drug found during clinical development. The drug was administered at doses ranging from 1000 mg/day to 3000 mg/day and the study lasted between 16 and 22 weeks for each participant.

One patient below 18 years was in accordance with the inclusion criteria of having epilepsy experiencing partial seizure, whether or not secondarily generalized, that were classifiable according to the International Classification of Epileptic Seizure and having at least three and no more than forty-two partial seizures over a 3-month historical baseline, while taking at least one but no more than two concomitant marketed antiepileptic drugs at stable dose. The subject was a 17 years old female patient receiving 1000 mg of Keppra per day. She experienced no AEs.

4. A Double-Blind, Placebo-Controlled, Randomized Study: 16-Week Evaluation Of The Efficacy And Safety Of Levetiracetam (Lev) As Add-on Therapy In Adults And Adolescents Older Than 16 Years Suffering From Partial Seizures

The objective of this double blind, randomized (1:1), placebo-controlled, multicenter, parallel group study was to evaluate the clinical efficacy and safety of Keppra when used as an add-on therapy in adult and adolescent Chinese subjects older than 16 years. The study period covered 20 weeks and included a retrospective historical baseline, randomization, the 16-week treatment period and either down titration for up to four weeks or a switch to long-term Levetiracetam therapy.

Thirteen patients in the levetiracetam group and nine in the placebo group were younger than 18 years (mean ages were 15.8 and 16.3 respectively), and fulfilled the inclusion criteria of having epilepsy with partial onset seizures (classifiable according to the ILAE classification of epileptic seizures) and having had at least eight partial seizures with or without secondary generalization (type IA, IB or IC) during the 8- week historical baseline period. Neither of them had been exposed to more than two classical stable AEDs before the selection visit. None of the subjects reported any AEs during the course of the study.

5. K.E.E.P.E.R. (Keppra Epilepsy Evaluation Of Patient Time To Response). A Phase Iv, Open-Label, Multi-Center, Community-Based Trial Studying The Safety And Efficacy Of Levetiracetam As Add-On Therapy In Adult Patients With Treatment-Resistant, Partial-Onset Epilepsy

This open-label multicenter study aimed to gather additional data on the safety and tolerability of the administration of LEV used as an add-on therapy in patients with partial onset seizures in community-based practices, and to measure the seizure reduction effect at the protocol-determined final doses (up to 3,000 mg/day).

Subjects underwent a 16 weeks treatment period, including four weeks of dose adjustment and a 12 week period receiving the target dose. After completion of the study, patients could continue to receive levetiracetam by conversion to prescription. For purposes of evaluation, the patient's dose remained stable after Visit 3 unless, in the investigator's opinion, a dosage modification was clinically necessary to achieve maximum benefit or was of medical concern.

Twenty-one patients in the levetiracetam group were <18 years (mean age = 16.5). They were about equally distributed in gender and 66.7% were of Caucasian descent. Nine of these patients (or 42.9%) reported at least one adverse event. Drug related adverse events were observed in 8 patients (38.1%). In two subjects (9.5%) 3 adverse events leading to premature discontinuation were observed: one patient reported gastrointestinal distress with nausea and vomiting while the other reported increased seizure activity. None were serious adverse events.

6. Anwendung Der In Deutschland Zugelassenen Keppra(R) – Tabletten Als Zusatzbehandlung Bei Erwachsenen Patienten Mit Fokalen Epilepsien

In this observational study, meant to gather data relating to the efficacy, tolerability and undesirable effects of Keppra, thirty-four patients were younger than 18 years (mean age was 14.6 years). 15 of the subjects were males. The product dose was at study start on average 1052.8 mg, at the intermediate visit it was 1844.4 mg and at study end 2270.3 mg. The minimum treatment duration was 3 months.

Three of the under eighteen subjects reported at least one AE. 2 of them suffered from asthenia, one from convulsions and one from pneumonia (which was a SAE).

7. A Phase IV, Open-Label, Multi-Center Community-Based Trial Studying The Safety And Efficacy Of Keppra. As Adjunctive Therapy In Adult Patients With Uncontrolled Partial Epilepsy. S.K.A.T.E.: Safety Of Keppra. As Adjunctive Therapy In Epilepsy

This multi-center open-label uncontrolled trial, focusing on the add-on therapeutic use of Keppra, aimed to evaluate the efficacy of Keppra in community-based practice and to further assess its safety. Furthermore, the optimal dose in daily clinical practice within the dose range 1000-3000 mg was to be assessed. Subjects, who were to be 16 years or older and experiencing partial (secondarily generalized) ICES classifiable seizure, would be treated for sixteen to twenty-two weeks. Participants also had to have at least one and no more than fourteen partial seizures per month as averaged over a 3-month historical baseline, and be taking at least one but no more than two concomitant marketed AEDs at stable dose.

The treatment consisted of a starting dose of 1000 mg/day for every subject. Over the first 4 weeks, this dose could be increased by 1000 mg/day every 2 weeks depending on the investigators' assessment of seizure control and tolerability, up to a maximum of 3000 mg/day.

In total 42 participating subjects were younger than 18 years with a mean age of 16.2 years. 40.5% of the subjects were male, while those of Caucasian descent made up 83.3% of the group. Seventeen patients (40.5%) reported at least one AE, and 38.1% reported a drug related AE. Three patients (7.1%) prematurely discontinued the study due to adverse events (somnolence, aggression and mental disorder). The latter was also a serious adverse event.

8. Bridging Study Of L059 (Levetiracetam) In Patients With Epilepsy By Double Blind Method

This trial (multicenter, double-blind, randomized, placebo controlled study with 3 parallel groups) was meant to evaluate the efficacy and safety of levetiracetam in treatment of refractory epileptic patients with partial onset seizures in the Japanese population, whom were being treated with one to three standard anti-epileptic drugs.

Patients were to receive either 1000 mg/day, 3000 mg/day or placebo in addition to their normal AEDs. Study medication was up-titrated during a 4-week titration period to reach the target daily dosage that was maintained during a 12-week evaluation period. Afterwards subjects went through either a 4-week withdrawal (down-titration) or a 6-week transition period to next follow-up study N01020.

Patients deemed fit for inclusion had to experience simple and/or complex partial seizures with or without secondary generalization, and have a minimum of twelve partial seizures during the 12-week baseline period with at least 2 seizures every four weeks.

Amongst the study population were eleven subjects <18 Years. Three were part of the placebo group, two of the LEV 1000 mg group and six of the 3000 mg group. The mean ages in each group were 16.3, 17.0 and 16.0 respectively. Nine patients were of male gender.

All patients reported at least one adverse event, 2 patients of the levetiracetam 3000 mg group reported drug related adverse events: Blood alkaline phosphatase increased and Urinary occult blood positive in one patient each. None of the adverse events led to early discontinuation; one patient reported a serious adverse event in the placebo group: pneumonia NOS.

IX. CONCLUSION

The MAH presented additional data on the safety and tolerability of levetiracetam on 125 patients below the age of 18 years which were on a regime of levetiracetam at doses between 1000 and 3000 mg/day. The exposure durations ranged from sixteen weeks to one year.

In total fifty-one patients (or 41%) reported at least one AE. 28 patients (22%) reported AEs which were considered to be drug-related.

No unknown types of adverse event were uncovered during the study review, as most were nervous system or psychiatric disorders. All AEs had already been reported in previously submitted clinical trials and are listed in levetiracetam Summary of Product Characteristics.

In conclusion, since also those patients cannot be taken into account for the evaluation of efficacy, the MAH considers that there is no change in levetiracetam's registered risk-benefit assessment in paediatric patients based upon this additional set of data collected in children younger than 18 years.

X. CHMP CONCLUSION

The MAH's conclusions are corroborated. None of the submitted studies seem to indicate apparent problems in subjects <18 years of age. One should of course keep in mind that this conclusion is based on rather limited data.

It is thus the CHMP opinion that the MAH can be considered to have fulfilled its obligations with regard to article 45 of the paediatric regulation EC/1901/2006. As a result, the present FUM can be can be considered as fulfilled.