HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 June 2010

KEPPRA 100 mg/ml oral solution
150 ml bottle with a 1 ml syringe, graduated every 0.05 ml, for oral administration
(CIP code: 398 276-5)

KEPPRA 100 mg/ml oral solution
150 ml bottle with a 3 ml syringe, graduated every 0.1 ml, for oral administration
(CIP code: 398 275-9)

Applicant : UCB PHARMA

levetiracetam
ATC code: N03AX14

List 1

Date of Marketing Authorisation and amendments for KEPPRA oral solution (centralised procedure): 03/03/2003, 13/09/2005, 27/04/2006, 07/08/2006, 02/09/2009 (Extension of indication: As adjunctive therapy, in the treatment of partial onset seizures with or without secondary generalisation in **infants from 1 month of age and in children under 4 years of age** with epilepsy)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Levetiracetam

1.2. Indications

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.

1.3. Dosage

“The oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe, an adaptor for the syringe and instructions for use in the package leaflet are provided with KEPPRA.
The daily dose is administered in two equally divided doses."[…]

"• Add-on therapy
[…]
Infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg
The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.
Dosage in children 50 kg or greater is the same as in adults.
The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.
Dosage recommendations for infants from 6 months of age, children and adolescents (see SPC)

Infants from 1 month to less than 6 months
The initial therapeutic dose is 7 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every two weeks. The lowest effective dose should be used.
Infants should start the treatment with KEPPRA 100 mg/ml oral solution.
The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight and dose.
Dosage recommendations for infants less than 6 months (see SPC)

Patients with renal impairment
The daily dose must be individualised according to renal function (see SPC).

Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m^2."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	Nervous system
N03	Antiepileptics
N03A	Antiepileptics
N03AX	Other antiepileptics
N03AX14	Levetiracetam

2.2. Medicines in the same therapeutic category

Not applicable

2.3. Medicines with a similar therapeutic aim (indications, see SPC)

Antiepileptics indicated as monotherapy or in combination in the treatment of partial onset seizures with or without secondary generalisation in infants and/or children

- Tablets and oral solutions:

Carbamazepine - TEGRETOL, tablet and oral suspension

Valproic acid - DEPAKINE, tablet and oral solution

Clonazepam - RIVOTRIL, tablet and oral solution

- Tablets (pharmaceutical forms unsuitable for children under 6 years of age):

Oxcarbazepine - TRILEPTAL (from 6 years of age)

Phenytoin - DI-HYDAN, tablet

Phenobarbital - GARDENAL, tablet

Primidone - MYSOLINE, tablet

Antiepileptics indicated in combination in the treatment of partial onset seizures with or without secondary generalisation

Lamotrigine - LAMICTAL, dispersible or chewable tablet (from 2 years of age)

Clobazam - URBANYL, hard capsule and tablet (unsuitable for children under 6 years of age)

Antiepileptic indicated as monotherapy following failure of previous treatment or in combination in the treatment of partial onset seizures with or without secondary generalisation

Topiramate - EPITOMAX, hard capsule and tablet (from 2 years of age)

Antiepileptic indicated in combination in the treatment of resistant partial onset seizures, with or without secondary generalisation, when all the other appropriate therapeutic combinations have proved to be inadequate or not well tolerated

Vigabatrin - SABRIL, tablet and granules for oral solution (infants and children)

3. ANALYSIS OF AVAILABLE DATA

The clinical data presented relate solely to the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children less than 4 years of age with epilepsy.

3.1. Efficacy

The efficacy and tolerance of levetiracetam for adjuvant therapy of partial onset epileptic seizures[1] in children between 1 month and 4 years of age were evaluated in comparison with placebo in a randomised, double-blind, phase III study (study N 01009[2]). The study was carried out in 13 countries, between October 2004 and January 2007.

Methodology

After a 9-day preinclusion phase, 116 patients were randomised for a 5-day double-blind period: levetiracetam (n = 60), placebo (n = 56).
Treatment was initiated at a dosage of 20 mg/kg/day (between 1 and 6 months) or 25 mg/kg/day (between 6 months and 4 years). The dosage was increased from the second day: 40 mg/kg/day (between 1 and 6 months) or 50 mg/kg/day (between 6 months and 4 years).

The patient inclusion criteria comprised:
- age over 1 month and under 4 years
- a diagnosis of refractory partial onset seizures
- fixed-dose treatment with one or two antiepileptic agents in the 2 weeks prior to inclusion
- at least two partial onset seizures per week in the 2 weeks prior to inclusion
- a pre-randomisation video EEG recording showing at least two partial onset seizures with or without secondary generalisation (associated with a clinical event in children over 6 months of age)

The primary endpoint was the percentage of responders, defined as those having an at least 50% reduction in mean daily partial-onset-seizure frequency calculated over 48 h of video EEG recording compared to baseline.

[1] Defined according to the International League Against Epilepsy classification. http://www.ilae-epilepsy.org/Visitors/Centre/ctf/CTFoverview.cfm.
[2] Pina-Garza JE, Nordli DR, Rating D et al. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. Epilepsia 2009;20(5):1141-1149.

Results

The mean age of the patients was 23 months:

Table 1: Distribution of the patients by age group

Age (months)	Levetiracetam (n = 60)	Placebo (n = 56)
	n (%)	n (%)
< 6	4 (6.7)	4 (7.1)
6 to 12	8 (13.3)	7 (12.5)
12 to 24	20 (33.3)	18 (32.1)
24 to 48	28 (46.7)	27 (48.2)

Table 2: Concomitant administration of antiepileptics

Number	Levetiracetam (n = 60)		Placebo (n = 56)	
	n	%	n	%
1	13	21.7	12	21.4
2	43	**71.7**	39	**69.6**
> 2	4	6.7	5	8.9

Table 3: Concomitant antiepileptic treatments

Antiepileptic	Levetiracetam (n = 60)		Placebo (n = 56)	
	n	%	n	%
Valproate	25	41.7	21	37.5
Phenobarbital	22	36.7	18	32.1
Topiramate	21	35.0	16	28.6
Oxcarbazepine	14	23.3	8	14.3
Vigabatrin	8	13.3	11	19.6
Clobazam	7	11.7	3	5.4
Carbamazepine	5	8.3	13	23.2
Clonazepam	3	5.0	9	16.1

The median initial daily frequency of partial onset seizures (48 h video EEG) was 15.2 in the levetiracetam group and 6.8 in the placebo group.

The mean dosage of levetiracetam after titration (24 h) was 40.5 mg/kg/day in the children under 6 months of age and 50.5 mg/kg/day in the children aged 6 months or over.

The patients analysed on an $ITT_{modified}$ basis (n = 109) had had at least 24 h of usable video recording or less than 24 h with discontinuation of therapy because of insufficient efficacy or loss of efficacy (non-responders).
Three patients discontinued the treatment in the placebo group and two patients in the levetiracetam group.

The percentage of responders was higher in the levetiracetam group (43.1%) than in the placebo group (19.6%): OR 3.11 95% CI [1.22; 8.26].
The median reduction in the number of partial onset seizures on levetiracetam (4.77) differed from that observed on placebo (0.13): difference of 5.0 95% CI [2.2; 8.0].

At least one adverse event was reported in 55% of the patients in the levetiracetam group and 44.6% of the patients in the placebo group. Two patients in the levetiracetam group (*versus* one patient on placebo) discontinued the treatment because of adverse events.

The most frequent adverse events (> 10%) were: drowsiness (13.3% in the levetiracetam group versus 1.8% in the placebo group) and irritability (5% *versus* 0%).

A treatment-related event was reported in 21.7% of the patients on levetiracetam versus 7.1% on placebo: drowsiness (8.3% *versus* 1.8%), irritability (5% *versus* 0%).

3.2. Open follow-up N01148 (interim analysis)

Two hundred and fifty five patients were included in a 48-week follow-up of the efficacy and tolerance of levetiracetam; 75% of the patients had previously been included in study N01009 or in study N01103 carried out in children between 4 and 16 years of age. 152 patients were between 1 month and 4 years of age. The treatment was initiated in an 8-week titration period. The optimised dosage was between 20 and 80 mg/kg/day.
The median initial daily frequency of partial onset seizures was 17.25 in the group aged 1 month to 4 years and 1.17 in the group aged 4 to 16 years.

The percentage of responders was 53.8% (71/132) in the group aged 1 month to 4 years and 69.1% (65/94) in the group aged 4 to 16 years. The median reduction in the number of partial onset seizures on levetiracetam was 3.44 in the group aged 1 month to 4 years (n = 134) and 0.39 in the group aged 4 to 16 years (n = 95).

One hundred and eighty patients (70.6%) completed the 48-week follow-up. Premature discontinuation of treatment was observed in 29.4% (75/255) of the patients: 36.2% of the children aged 1 month to 4 years, 19.4% of the children aged 4 to 16 years. Discontinuation of treatment because of insufficient efficacy or loss of efficacy was observed in 8.6% of the children aged 1 month to 4 years and 4.9% of the children aged 4 to 16 years, and discontinuation because of an adverse event was observed in 15.1% of the children aged 1 month to 4 years and 6.8% of the children aged 4 to 16 years.
At least one treatment-related adverse event was observed in 39% of the children aged 1 month to 4 years. The commonest adverse events were: irritability (7.9%), convulsions (6.6%), drowsiness (6.6%), motor hyperactivity (3.3%) and sleep disturbances (3.3%).
There were three deaths. Two of them, in which a connection with the treatment was considered doubtful, occurred in two children who showed cerebral oedema. The third was considered to be unrelated to the treatment.

3.3. Adverse effects

3.2.1. Data from clinical trials

The pooled data from the 168 children aged 1 month to 4 years come from follow-up study N01009 and N01148 (n = 154) and from follow-up study N01052 and N157 (n = 14). An interim analysis was carried out in September 2007. A duration of exposure exceeding 24 weeks was reported for 74.4% of the patients.
The mean age of the children was 23 months (1 to 47 months): 34.5% of the children were 12 to 24 months of age, 44.6% 24 to 48 months of age, 13.1% 6 to 12 months of age, and 7.7% 1 to 6 months of age. Seventy seven per cent were caucasians. The majority of the patients received 2 antiepileptic agents.
38% of the patients between 1 month and 4 years of age discontinued the treatment prematurely: insufficient efficacy or loss of efficacy (13.1%), adverse event (10.7%). In most of these discontinuation cases, discontinuation occurred during the first 24 weeks.

At least one treatment-related event occurred in 43% of the children. The most frequently reported ones were: drowsiness (8.9%), convulsions (7.1%), and irritability (10.1%). Nervous system disorders were reported in 23.8% of cases, psychiatric disorders in 18.5% of cases, and gastrointestinal disorders in 8.3% of cases.
One serious adverse event at least was reported in 29% of patients: infection 10%, nervous system disorders 15.5% (epilepsy 10%).

3.2.2. Data from pharmacovigilance follow-up

Between the launch of the product (April 2000 in the USA) and September 2009, the patient exposure was estimated to be 3,639,970 patient-years. The paediatric population (< 16 years) is estimated to account for 11.7% of the patients exposed or 261,985 patient-years.
The collected tolerance data showed the most frequent adverse events possibly related to the treatment to be: asthenia, drowsiness and behavioural problems, and gastrointestinal disorders. Inappetence, weight gain, and sight problems were also observed. Haematological disorders were reported (0.13/100 patient-years).
Thirty four cases of severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) have been identified since launch, representing an incidence of 0.09/10,000 patient-years. A proposed change to the SPC was submitted by the company on 15 February 2010.
One hundred and sixty eight adverse events were reported in 88 children aged 1 month to 4 years. The cumulative data do not show any particular signal in regard to tolerance in this age group.

The data from the last periodic tolerance update report (01/12/2008 - 31/12/2009) did not result in any change in the product's tolerance profile. The number of patients exposed to levetiracetam in this period is estimated at 689,571 patient-years. 25 of the 1810 reported cases related to children aged 1 month to 4 years.

As part of the risk management plan, haematological disorders, behavioural disorders, and aggravation of the epileptic seizures during treatment are the subject of a pharmacovigilance follow-up, as are the long-term impact of the treatment on learning, intellectual development, growth, endocrine function, puberty, and patient fertility. A study is to be performed in children under 12 months of age.

3.4. Conclusion

The efficacy of levetiracetam in combination in the treatment of partial onset seizures resistant to one or two antiepileptics was demonstrated in a randomised double-blind study versus placebo in children less than 4 years of age. In 71% of the children, there was concomitant prescription of two other antiepileptics. The concomitant antiepileptics were: valproate 40%, phenobarbital 34%, and topiramate 32%. The median frequency of partial onset seizures on inclusion was 15.2/day in the levetiracetam group versus 6.8/day in the placebo group.
The percentage of responders (an at least 50% reduction in mean daily frequency of partial onset seizures recorded with EEG over a period of 48 h) after 5 days of treatment was higher with levetiracetam (43.1%) than with placebo (19.6%). Continuation of this study on an open basis suggests that levetiracetam's effect on seizure reduction persists even though 36% of the patients discontinued the study prematurely.
The most frequently observed adverse effects were drowsiness and irritability.

The cumulative pharmacovigilance data do not show any particular signal in regard to tolerance in this age group.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Epileptic seizures are symptoms of a very diverse array of diseases. Epilepsy, defined as – generally spontaneous – repetition of these seizures over the medium and long term, can markedly impair the patient's quality of life. In children, epilepsy and its treatment can have a major impact on the various stages of cognitive, behavioural, and social development.

These proprietary products fall under the category of symptomatic treatment.

The efficacy/adverse effect ratio of these proprietary products as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children under 4 years of age with epilepsy is high.

There are treatment alternatives to these proprietary products.

Public health benefit:

Partial-onset epilepsy is a common disease, and the repetition of the seizures in some patients can markedly impair their quality of life. In children, epilepsy is accompanied in particular by cognitive development problems, learning difficulties, and behavioural problems. Overall, partial onset epilepsy represents a moderate public health burden. However, the burden represented by the population of infants and children less than 4 years of age with partial onset epilepsy is small due to the limited number of patients concerned.

Preventing functional and cognitive impairment and its consequences in the children, a task in which KEPPRA could be of assistance, is a public health need that is an established priority (Public Health Law 2004). This need remains insofar as drug-resistant partial onset epilepsy is still common and the cause of considerable disability, particularly in the case of children, for whom there are few well-tolerated treatments.

It is not possible, on the basis of the data available, to fully assess the expected impact of KEPPRA used in combination in this indication. However, in view of the reduction in seizure frequency obtained with KEPPRA, its good tolerability, and its formulation appropriate for young children, KEPPRA can be assumed to have an effect on morbidity (including quality of life). The impact of the treatment on other parameters such as the child's cognitive development, education, and family life is not documented.

Nevertheless, KEPPRA should be able to make an additional contribution towards meeting the identified public health need.

Consequently, KEPPRA is expected to benefit public health in this indication. Because of the size of the population concerned, this benefit can only be low.

The actual benefit of these proprietary products as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children under 4 years of age with epilepsy is substantial.

Assignment of actual benefit in the other indications does not apply, insofar as the presentations of KEPPRA oral solution with a 1 ml syringe graduated every 0.05 ml and 3 ml syringe graduated every 0.1 ml are presentations of the oral solution that are specifically tailored for paediatric use.

4.2. Improvement in actual benefit (IAB)

Against a background in which the antiepileptics used in children and the pharmaceutical forms of these antiepileptics have not been adequately evaluated, KEPPRA 100 mg/ml oral solution with 1 ml and 3 ml syringes provides a moderate improvement in actual benefit (IAB III) as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children under 4 years of age, in the same way as KEPPRA 100 mg/ml oral solution with a 10 ml syringe in children over 4 years of age in this indication.

4.3. Therapeutic use[3,4,5,6]

The management of partial onset epilepsy in children less than 4 years of age calls for multidisciplinary medical and psychosocial monitoring.

In France, valproic acid, carbamazepine, benzodiazepines, phenobarbital, and phenytoin are indicated as first-line therapy in symptomatic or probably symptomatic partial onset epilepsy in children less than 4 years of age. Vigabatrin, levetiracetam, and lamotrigine are also prescribed, but are not indicated for monotherapy. Carbamazepine is used with caution in these children on account of the risk of increasing the frequency of associated spasms.
Treatment of idiopathic partial onset epilepsy is based on monotherapy with valproate or a benzodiazepine. Carbamazepine is rarely prescribed, on account of the risk of aggravation in certain cases of partial onset epilepsy.
It is recommended that bitherapy be used only after at least two monotherapies have failed. It is not possible to say that a particular drug combination should be preferred, as there are insufficient data available. The combination valproate/lamotrigine is subject to precise rules governing its prescription, on account of the risk of cutaneous toxicity connected with the use of lamotrigine.
Vigabatrin is indicated in the treatment of drug-resistant partial onset epilepsy in particular if it is associated with spasms. The risks of the occurrence of irreversible narrowing of the visual field limit its prescription.
Patients may benefit from the addition of topiramate, lamotrigine, or levetiracetam, which are further alternative treatments.
When it comes to choosing a combination of two antiepileptics, the preference is for use of non enzyme-inducing ones, with rapid titration and avoidance of administration at midday. The use of a combination of more than two antiepileptic medicines is not recommended.
It is recommended that the epilepsy and its treatment be reassessed at a specialist centre in the event of the failure of one or more bitherapies.

Use of the injectable form is recommended in cases of acute symptomatic epileptic seizure if use of an injectable benzodiazepine is inadvisable. It is also an alternative dosage form when administration by the oral route is impracticable.

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[3] Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disorder, 2007; 9(4): 353-412.

[4] Glauser T, Ben-Menachem E et al. International League Against Epilepsy Treatment Guidelines : Evidence-based analysis of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Epilepsia, 2006 ; 47:1094-1120.

5 National Institute for Clinical Excellence. The epilepsies, the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline 20, October 2004.

6 Conférence de consensus. Prise en charge des épilepsies partielles pharmaco-résistantes [Consensus conference. Management of drug-resistant partial onset epilepsy]. March 2004. ANAES, FFN and LFCE.

4.4. Target population

The target population of KEPPRA can be estimated from the following data:

- Children aged 1 month to 4 years on 1 January 2009[7]: 3,220,892 children
- On the basis of a Finnish cohort[8] of 329 children aged 0 to 15 years, the prevalence of epilepsy in these children is estimated to be 2 per 1000, or about 6400 children. The prevalence of partial onset epilepsy in this age group can be estimated at 21%, or about 1300 children.

- According to expert opinion, 20 to 30% of paediatric partial onset epilepsy cases are drug-resistant.

According to these data, the number of children aged 1 month to 4 years who might receive KEPPRA as adjunctive therapy after the failure of monotherapy is about 400.

4.5. Transparency Committee recommendations

The transparency Committee recommends that the proprietary products KEPPRA 100 mg/ml oral solution with a 1 ml syringe graduated every 0.05 ml and KEPPRA 100 mg/ml oral solution with a 3 ml syringe graduated every 0.1 ml be included on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services, in the indication "as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children under 4 years of age with epilepsy."

4.5.1 Packaging

The packaging of these proprietary products is appropriate in the indication “as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in infants from 1 month of age and in children under 4 years of age with epilepsy”.
However, the Committee regrets the graduation in ml of the dosing syringe recommended by the EMA, which means that conversion calculations have to be performed, laying open the possibility of dose errors.

The packaging of these proprietary products is not appropriate in the other indications.

4.5.2 Reimbursement rate: 65%.

7 http://www.insee.fr/fr/ppp/bases-de-donnees/donnees-detaillees/bilan-demo/xls/pyramide-des-ages-2010.xls

8 Eriksson KJ. Koivikko MJ. Prevalence, classification and severity of epilepsy and epileptic syndromes in children Epilepsia 1997 Dec.; 38(12):1275-82.