HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 February 2007

KEPPRA 250 mg film-coated scored tablets
Box of 60 tablets (CIP: 356 013-6)
KEPPRA 500 mg film-coated scored tablets
Box of 60 tablets (CIP: 356 016-5)
KEPPRA 1,000 mg film-coated scored tablets
Box of 60 tablets (CIP: 356 022-5)
KEPPRA 100 mg/ml drinkable suspension
1 300-ml vial (CIP: 370 238-1)
KEPPRA 100 mg/ml solution to be diluted for infusion
Box of 10 vials (CIP: 375 893-8)

Applicant : UCB PHARMA SA

levetiracetam
List I
N03AX14
Date of Marketing Authorisation:
KEPPRA 250 mg, 500 mg, 1,000 mg film-coated scored tablets: September 29, 2000;
KEPPRA 100 mg/ml drinkable suspension: March 3, 2003
KEPPRA 100 mg/ml solution to be diluted for infusion: March 29, 2006

Revision of Marketing Authorisation:
KEPPRA 250 mg, 500 mg, 1000 mg film-coated tablets, and KEPPRA 100 mg/ml drinkable suspension: September 13, 2005 (Extension of indication for children aged four or over).
April 27, 2006 (Extension of indication for forms of juvenile myoclonia)
August 07, 2006 (Extension of indication for monotherapy in adults)

Reason for request:
KEPPRA 250 mg, 500 mg, 1000 mg film-coated scored tablets, KEPPRA 100 mg/ml drinkable suspension: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the new indications "Monotherapy in the treatment of partial seizures with or without secondary generalisation in adult patients recently diagnosed with epilepsy" and "As part of combination therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy".

KEPPRA 100 mg/ml solution to be diluted for infusion: Inclusion on the list of medicines approved for use by hospitals in the new indications "Monotherapy in the treatment of partial seizures with or without secondary generalisation in adult patients recently diagnosed with epilepsy" and "As part of combination therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy".

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Levetiracetam

1.2. Indications

As part of adjunctive therapy for epileptic patients in the treatment of partial seizures with or without secondary generalisation in adults and in children aged four and over.

As monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 and over recently diagnosed with epilepsy.

As part of adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 and over with juvenile myoclonic epilepsy.

Keppra solution to be diluted for infusion is an alternative for patients temporarily unable to take oral drugs.

1.3. Dosage

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

Monotherapy
Adults and adolescents from 16 years of age
The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending on the clinical response. The maximum dose is 1500 mg twice daily.

Add-on therapy
Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more:
The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.
Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Elderly (65 years and older):
Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Patients with renal impairment” below).

Children aged 4 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 on 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 children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg (1)	150 mg twice daily	450 mg twice daily
20 kg (1)	200 mg twice daily	600 mg twice daily
25 kg (1)	250 mg twice daily	750 mg twice daily
From 50 kg (2)	500 mg twice daily	1500 mg twice daily

(1) Children 20 kg or less should preferably start the treatment with Keppra 100mg/ml oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.

- Infants and children less than 4 years

Keppra is not recommended for use in children below 4 years of age due to insufficient data on safety and efficacy.

- Patients with renal impairment

The daily dose must be individualised according to renal function (SmPC).

Patients with hepatic impairment
A dose adjustment is recommended in case of severe hepatic impairment (SmPC).

KEPPRA 100 mg/ml solution to be diluted for perfusion:
Patients may be switched from the oral to intravenous mode of administration and vice versa immediately without checking plasma levetiracetam levels. The daily dose and frequency of administration must remain the same.

KEPPRA solution to be diluted must only be administered via the intravenous route, and the recommended dose must be diluted in at least 100 ml of a compatible solvent and administered intravenously over 15 minutes.

No data is available on intravenous administration of levetiracetam over more than four days.

2 REMINDER OF THE COMMITTEE'S OPINION AND CONDITIONS OF INCLUSION

Opinion of the Committee of 7 February 2001

KEPPRA has a significant clinical benefit.
Given its pharmacokinetic profile and the fact that levetiracetam is well tolerated, KEPPRA doesn't offer improvement in clinical benefit compared to NEURONTIN, but offers a minor (grade IV) improvement compared to other second-line anti-epileptics used in adjunctive therapy.

Approval for inclusion of KEPPRA 250, 500 and 1,000 mg film-coated tablets on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in all the marketing authorisation's indications.

Opinion of the Committee of 19 July 2006

The clinical benefit offered by these proprietary products is significant in the new indication "As part of adjunctive therapy for epileptic patients in the treatment of partial seizures with or without secondary generalisation in children aged four or over".

Given the low risk of pharmacokinetic interaction between levetiracetam and the poor availability of third-generation anti-epileptic drugs for children, the oral forms of KEPPRA offer a moderate (level III) improvement in actual benefit in the new indication.

KEPPRA 100 mg/ml drinkable solution, an addition to the KEPPRA range comprising 250 mg, 500 mg and 1000 mg film-coated tablets, offers no improvement in actual benefit (level V) for adults.

Considering the absence of third-generation anti-epileptic injectable formulation, KEPPRA 100 mg/ml solution to be diluted for infusion offers a minor (level IV) improvement in clinical benefit in this indication.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2006)

N : Nervous system
N03 : Anti-epileptics
N03A : Anti-epileptics
N03AX : Other anti-epileptics
N03AX14 : Levetiracetam

3.2. Medicines in the same therapeutic category

Not applicable.

3.3. Medicines with a similar therapeutic aim

Anti-epileptics for use in monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over recently diagnosed with epilepsy:

- Phenytoin - DI-HYDAN 100 mg scored tablets (for infants, children and adults);
- Primidone - MYSOLINE 250 mg scored tablets (for infants, children and adults);
- Gabapentin - NEURONTIN 600 mg and 800 mg film-coated tablets and NEURONTIN 100 mg, 300 mg and 400 mg gelatin capsules (for adults and children over 12);
- Lamotrigine - LAMICTAL 2 mg dispersible tablets, LAMICTAL 5 mg, 25 mg, 50 mg, 100 mg, 200 mg tablets and dispersible tablets (for children over 2 and for adults).

Proprietary products available in drinkable form:

- Phenobarbital - GARDENAL 10 mg, 50 mg and 100 mg tablets – ALEPSAL 15 mg, 50 mg, 100 mg and 150 mg tablets – APAROXAL 100 mg tablets – KANEURON 5.4% drinkable solution; (for infants, children and adults)
- Carbamazepine - TEGRETOL 100 mg/5 ml drinkable suspension, TEGRETOL 200 mg scored tablets and TEGRETOL CR 200 mg and 400 mg film-coated tablets (for infants, children and adults)
- Valproic acid - DEPAKINE 200 mg and 500 mg enteric-coated tablets, DEPAKINE 57,64 mg/ml syrup, DEPAKINE 200 mg/ml drinkable solution - DEPAKINE CHRONO 500 mg controlled-release tablets – MICROPAKINE CR 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg (for infants, children and adults)
- Oxcarbazepine - TRILEPTAL 150 mg, 300 mg, 600 mg film-coated tablets and TRILEPTAL 60 mg/ml drinkable suspension (for children aged over six and adults)
- Clonazepam – RIVOTRIL 2 mg tablets with two break bars, RIVOTRIL 2.5 mg/ml drinkable solution (for infants, children and adults);

Injectable forms:

- Valproic acid - DEPAKINE 400 mg/4 ml IV injectable form (for infants, children and adults);
- Fosphenytoin - PRODILANTIN 75 mg/ml injectable solution (for adults and children over five);
- Phenobarbital - GARDENAL 40 mg/2 ml and 200 mg/4 ml injectable forms (for infants, children and adults).

Anti-epileptics indicated for use in adjunctive therapy of generalised seizures:

1/ Drugs indicated for the treatment of absence seizures:

- Ethosuximide: ZARONTIN 250 mg capsules and ZARONTIN 250 mg/5 ml syrup (for infants, children and adults)
- Valproic acid - DEPAKINE 200 mg and 500 mg enteric-coated tablets, DEPAKINE 57.64 mg/ml syrup, DEPAKINE 200 mg/ml drinkable solution - DEPAKINE CHRONO 500 mg controlled-release tablets and DEPAKINE 400 mg/4 ml IV injectable form (for infants, children and adults)
- Lamotrigine – LAMICTAL 2 mg dispersible tablets, LAMICTAL 5 mg, 25 mg, 50 mg, 100 mg, 200 mg tablets and dispersible tablets (for children aged over 2 and for adults)
- Clobazam - URBANYL 10 mg scored tablets and URBANYL 20 mg tablets (for infants, children and adults)
- Clonazepam – RIVOTRIL 2 mg tablets with two break bars, RIVOTRIL 2.5 mg/ml drinkable solution (for infants, children and adults);

2/ Drugs indicated for the treatment of myoclonic seizures:

- Ethosuximide: ZARONTIN 250 mg capsules and ZARONTIN 250 mg/5 ml syrup (for infants, children and adults)
- Valproic acid - DEPAKINE 200 mg and 500 mg enteric-coated tablets, DEPAKINE 57.64 mg/ml syrup, DEPAKINE 200 mg/ml drinkable solution - DEPAKINE CHRONO 500 mg controlled-release tablets and DEPAKINE 400 mg/4 ml IV injectable form (for infants, children and adults)
- Clobazam - URBANYL 10 mg scored tablets and URBANYL 20 mg tablets (for infants, children and adults)
- Clonazepam – RIVOTRIL 2 mg tablets with two break bars, RIVOTRIL 2.5 mg/ml drinkable solution (for infants, children and adults);
- Lamotrigine – LAMICTAL 2 mg dispersible tablets, LAMICTAL 5 mg, 25 mg, 50 mg, 100 mg, 200 mg tablets and dispersible tablets (for children aged over 2 and for adults)

3/ Drugs indicated for the treatment of tonicoclonic seizures:

- Phenobarbital - GARDENAL 10 mg, 50 mg and 100 mg tablets and GARDENAL 40 mg/2 ml and 200 mg/4 ml injectable forms (- ALEPSAL 15 mg, 50 mg, 100 mg and 150 mg tablets – APAROXAL 100 mg tablets – KANEURON 5.4% drinkable solution (for infants, children and adults);
- Carbamazepine - TEGRETOL 100 mg/5 ml drinkable suspension, TEGRETOL 200 mg scored tablets and TEGRETOL CR 200 mg and 400 mg film-coated tablets (for infants, children and adults)
- Valproic acid - DEPAKINE 200 mg and 500 mg enteric-coated tablets, DEPAKINE 57.64 mg/ml syrup, DEPAKINE 200 mg/ml drinkable solution - DEPAKINE CHRONO 500 mg controlled-release tablets and DEPAKINE 400 mg/4 ml IV injectable form (for infants, children and adults)
- Clonazepam – RIVOTRIL 2 mg tablets with two break bars, RIVOTRIL 2.5 mg/ml drinkable solution (for infants, children and adults);
- Clobazam - URBANYL 10 mg scored tablets and URBANYL 20 mg tablets (for infants, children and adults)
- Phenytoin - DI-HYDAN 100 mg scored tablets (for infants, children and adults)

- Primidone - MYSOLINE 250 mg scored tablets (for infants, children and adults)
- Topiramate – EPITOMAX 15 mg and 25 mg gelatin capsules, EPITOMAX 25 mg, 50 mg, 100 mg and 200 mg tablets (for children over two and adults)
- Lamotrigine – LAMICTAL 2 mg dispersible tablets, LAMICTAL 5 mg, 25 mg, 50 mg, 100 mg, 200 mg tablets and dispersible tablets (for children aged over 2 and for adults)

4 ANALYSIS OF AVAILABLE DATA

The pharmaceutical company submitted the results of two pivotal studies:
- Study N01061[1] compared the efficacy of levetiracetam used in monotherapy with that of controlled-release carbamazepine in patients aged over 16 suffering from newly diagnosed partial epilepsy.
- Study N166 assessed the efficacy of levetiracetam versus placebo in patients suffering from generalised idiopathic epilepsy with myoclonic seizures. An open-label extension phase of study N166 is taking place at present (N167). The pharmaceutical company submitted interim results. They are not discussed in detail in this opinion.

4.1. New indication: "As monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over recently diagnosed with epilepsy": Study N01061

Objectives:
The aim of study N01061 was to demonstrate the non-inferiority of levetiracetam used in monotherapy compared with controlled-release carbamazepine in patients aged over 16 suffering from newly-diagnosed epilepsy and experiencing partial or generalised tonicoclonic seizures.

The analysis was carried out using a logistic regression model.

Non-inferiority was accepted if, for a 95% confidence interval, the lower limit of the absolute adjusted difference between the two groups (for the various types of seizures) of the percentage of patients experiencing no seizures after six months was greater than 15%.

Methodology:
Study N01061 was a randomised, double-blind, parallel-group study.

The efficacy and tolerance of levetiracetam administered at doses ranging from 1,000 mg to 3,000 mg divided into two equal daily doses were compared to those of controlled-release carbamazepine administered at doses ranging from 400 mg to 1,200 mg divided into two equal daily doses.

The study consisted of various phases:
- A one-week screening period, at the end of which patients were randomised.
- Treatment titration for two weeks.
- Dose stabilisation for one week.
- 26 weeks of assessment following by a 26-week maintenance phase.

Dose elevation in two stages was permitted for patients experiencing a seizure during the assessment phase up to a maximum of 3,000 mg for levetiracetam and 1,200 mg for controlled-release carbamazepine.

[1] Brodie MJ et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology February 2007 ; 68 : 402-408.

Inclusion Criteria:

- Patients aged over 16;
- Newly diagnosed epilepsy with partial or generalised tonicoclonic seizures;
- Patients experiencing at least two unprovoked seizures during the past year, one of which must have occurred in the three months prior to randomisation.

Patients who had previously been treated with an anti-epileptic (except for less than two weeks to treat a seizure) were excluded.

Primary endpoint: percentage of patients seizure-free after six months of treatment (optimum anti-epileptic dose).

Secondary endpoint considered for this opinion: percentage of patients seizure-free after one year of treatment (optimum anti-epileptic dose).

The results of the per-protocol analysis of this non-inferiority study are set out in the table below.

Results of study N01061

	Levetiracetam	**CR Carbamazepine**
N (per protocol)	237	235
Average age (years)	39.5	39.6
Percentage of patients seizure-free after six months	73%	72.8%
Absolute adjusted difference	0.2%	
95% CI.	[-7.8%; 8.2%]	
Percentage of patients seizure-free after one year	56.6% (N = 228)	58.5% (N = 224)
Absolute adjusted difference	- 1.8%	
95% CI.	[-10.8%; 7.2%]	

Primary endpoint: in this study, the efficacy of levetiracetam was significantly non-inferior to that of CR carbamazepine in terms of the percentage of patients seizure-free after six months of treatment.

The ITT analysis results confirmed the per-protocol results.

Secondary endpoint:
The efficacy of levetiracetam was significantly non-inferior to that of CR carbamazepine in terms of the percentage of patients seizure-free after one year of treatment.

78.9% of patients in the CR carbamazepine group were treated with a dose of 400 mg/day (optimum dose) and 70% of patients in the levetiracetam group were treated with a dose of 1,000 mg/day (optimum dose).

One of the main reasons for stopping treatment (46.2% of patients) was lack of efficacy: 50 patients in the levetiracetam group (17.5%) versus 29 patients in the CR carbamazepine group (10%).

Tolerance:
In the ITT population (N= 576, 291 patients in the CR carbamazepine group, 285 in the levetiracetam group) 2,093 adverse events were observed:

- 1,107 in 235 patients in the CR carbamazepine group, or 80.8% of the patients in this group (235/291);
- 986 in 227 patients in the levetiracetam group, or 79.6% of patients in this group (227/285).

The most frequent adverse events (≥ 10%) were:

	CR Carbamazepine	Levetiracetam
Headache	25.4 %	20.7 %
Fatigue	14.1 %	16.5 %
Vertigo	13.7 %	10.9 %
Nausea	10.7 %	< 10 %
Somnolence	< 10 %	11.2 %

Adverse events occurring at a rate of ≥ 5% were back pain, headache, nausea and weight gain, occurring more frequently in the CR carbamazepine group than in the levetiracetam group.

Adverse events occurring at a rate of ≥ 5% were depression and insomnia, occurring more frequently in the levetiracetam group than in the CR carbamazepine group.

Adverse events possibly linked to CR carbamazepine and occurring at a rate of ≥ 10% were headache (13.1%), fatigue (13.1%) and vertigo (11%).

Adverse events possibly linked to levetiracetam and occurring at a rate of ≥ 10% were fatigue (14.4%) and somnolence (11.2%).

Severe adverse events were observed in 10% of patients in the CR carbamazepine group versus 6.3% in the levetiracetam group: in both groups these were mainly psychiatric disorders and conditions of the skin and related tissue.

In the ITT population, 46.2% (266/576) of patients stopped treatment before the end of the study. 97 patients stopped treatment following an adverse event: 19.2% in the CR carbamazepine group (n = 56) versus 14.7% in the levetiracetam group (n = 42).

Conclusion:
Per-protocol analysis of the results of this study demonstrated the non-inferiority of the efficacy of levetiracetam used in monotherapy compared with that of CR carbamazepine used in monotherapy in terms of the percentage of patients experiencing no seizures after six months of treatment. These results were confirmed by the ITT analysis.

Almost 18% of patients being treated with levetiracetam stopped treatment as a result of inefficacy of levetiracetam in first-line monotherapy, compared with 10% in the CR carbamazepine group.

More patients stopped treatment following an adverse event in the CR carbamazepine group than in the levetiracetam group (19.2% versus 14.7%).

4.2. New indication: "As part of adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy": Study N166

Objectives:
The aim of study N166 was to assess the efficacy and tolerance of levetiracetam versus placebo in adjunctive therapy with another anti-epileptic treatment in patients aged over 12 suffering from generalised idiopathic epilepsy with myoclonic seizures.

Methodology:
Study N166 was a comparative, randomised, double-blind, parallel-group study (levetiracetam versus placebo).

The analysis was carried out using a logistic regression model.

The efficacy and tolerance of levetiracetam, administered at a rate of 3,000 mg per day divided into two equal daily doses, were assessed over the course of 12 weeks in patients suffering from generalised idiopathic epilepsy with myoclonic seizures and being treated with another anti-epileptic drug.

The study consisted of various phases:

- Eight-week baseline phase at the end of which patients were randomised; during this phase patients were treated with a placebo in a single-blind design.
- Levetiracetam titration phase lasting four weeks in which the dose was increased in stages of 1,000 mg a day for two weeks and then in stages of 2,000 mg a day for two weeks, with the final dose being 3,000 mg a day.
- 12-week assessment phase.

The dose could be reduced to 2,000 mg a day during the first week of the assessment phase.

Inclusion Criteria:

- Patients aged 12 to 65.
- Generalised idiopathic epilepsy with myoclonic seizures (type IIB): juvenile myoclonic epilepsy, juvenile absence epilepsy or epilepsy with generalised tonicoclonic seizures on waking up;
- The patients must have had one myoclonic seizure a day (type IIB) for at least eight days during the eight weeks prior to randomisation.
- Patients being treated with an anti-epileptic drug other than levetiracetam at stable doses for at least four weeks before the baseline phase of the study.

Primary endpoint: percentage of patients responding to treatment, defined by a reduction of at least 50% in the number of days a week during which they experienced IIB myoclonic seizures.

Secondary endpoints taken into consideration in this opinion:

- Percentage of patients responding to treatment in terms of the reduction in weekly frequency of IIB myoclonic seizures.
- Percentage of patients seizure-free.

Results:
Over 50% of the patients in each of the two groups were also taking valproic acid and over 25% were also taking lamotrigine. The other patients were also taking phenobarbitol or topiramate.

The results of the ITT analysis of this study are set out in the table below:

Results of study N166

	Levetiracetam	Placebo
N (ITT)	60	60
Average age (years)	25 [13.8 – 50.7]	26.8 [14.2 – 52.4]
Percentage of responders with a reduction of ≥ 50% in the number of days per week on which seizures occurred	58.3% (n = 35)	23.3% (n = 14)
	odds ratio = 4.77 (LEV vs PBO) 95% CI [2.12; 10.77)	
Percentage of responders with a reduction of ≥ 50% in the weekly frequency of myoclonic seizures	63.3 %	31.7%
	odds ratio = 3.73 (LEV vs PBO) 95% CI [1.75; 7.96]	
Percentage of patients experiencing no myoclonic seizures in a week	25% (n=15)	6.9% (n=4)
Percentage no seizure-free in a week	21.7 % (n=13)	3.4% (n=2)

Primary endpoint:

The percentage of patients experiencing a reduction of at least 50% in the number of days a week on which they had myoclonic seizures was significantly higher in the levetiracetam group than in the placebo group (58.3% versus 23.3%): patients taking levetiracetam as part of their anti-epileptic treatment had almost five times fewer days with seizures per week than patients being treated in monotherapy.

These results were confirmed by the per-protocol analysis.

None of the patients in the levetiracetam group stopped treatment because of lack of efficacy. In the placebo group, four patients stopped treatment during the study because of lack of efficacy.

Tolerance:

75% of patients in the levetiracetam group experienced adverse events during the treatment phase (titration phase plus assessment phase) versus 66.7% of patients in the placebo group.

The most common adverse events in the levetiracetam group compared to the placebo group were: vertigo, flu, pharyngitis, neck pain, somnolence and depression.
The percentage of adverse events possibly linked to treatment was 33.3% in the levetiracetam group and 30% in the placebo group. The most frequent of these adverse events were fatigue, dizziness, headache and somnolence.

Five patients experienced a serious adverse event during the study: four in the levetiracetam group and one in the placebo group. None of these serious adverse events was attributed to either of the two treatments.

17 patients in the ITT population stopped their treatment during the study: three patients in the levetiracetam group stopped treatment following an adverse event versus one patient in the placebo group.

Conclusions:

Analysis of the results of study N166 showed levetiracetam to be more effective than placebo in treating generalised idiopathic epilepsy with myoclonic seizures in patients aged over 12 when used as part of combination therapy. The percentage of patients responding to treatment, defined as the number of days a week on which seizures occurred, was significantly higher in the levetiracetam group than in the placebo group (58.3% versus 23.3%).

The percentage of adverse events possibly linked to treatment was similar in both groups (33.3% in the levetiracetam group and 30% in the placebo group).

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual Benefit

Epileptic seizures are widely varied symptoms of disease. Epilepsy, defined by the usually spontaneous recurrence of these seizures in the medium to long term can significantly impair the patients' quality of life.

These proprietary products come within the scope of preventive treatment.

The efficacy/safety ratio of these proprietary product is high in these indications.

These proprietary products are first-line products for the indication: "As monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 and over recently diagnosed with epilepsy".

They are second-line proprietary products for the indication: "As part of combination therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 and over with juvenile myoclonic epilepsy".

There are alternative drug treatments that could be used instead of these proprietary products.

Public Health Benefit
1/ Partial epilepsy is a common condition, and the repeated seizures suffered by some patients can markedly impair their quality of life. The burden on public health caused by partial epilepsy in adults is moderate.

There is a public health need as partial epilepsy is still common and causes significant disability.

The clinical data available and existing therapies (for first-line monotherapy) do not allow the possible impact of KEPPRA on morbidity, including the quality of life of the population being treated, to be quantified.

The proprietary product KEPPRA should be able to provide a supplementary response to the identified public health requirement.

However, as no information is available relating to public health criteria, there is not likely to be any public health benefit for this proprietary product in this indication.

2/ The burden relating to patients suffering from myoclonic seizures in the context of juvenile myoclonic epilepsy is low because it affects few patients.

A public health requirement can be fulfilled as juvenile myoclonic epilepsy is still a cause of major disability for which no other combination treatment is available.

In the light of the clinical data available, it is expected that this proprietary product will have a small impact in terms of morbidity and quality of life.

The proprietary product KEPPRA should be able to provide a supplementary response to the identified public health requirement.

Consequently, this product is expected to have a public health benefit. This benefit is low.

The actual benefit conferred by these proprietary products is substantial in the two new indications.

5.2. Improvement in actual benefit

Levetiracetam has a minor (IAB IV) improvement in actual benefit in terms of tolerance compared to CR carbamazepine used in monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over with recently diagnosed epilepsy.

Levetiracetam has a moderate (IAB III) improvement in actual benefit in the treatment of adults and children over 12 with juvenile myoclonic epilepsy.

5.3. Therapeutic use[2,3]

5.3.1. As monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over recently diagnosed with epilepsy.

Monotherapy is the first-line treatment recommended for newly or recently diagnosed partial epilepsy, particularly carbamazepine or valproic acid, as the risk/benefit ratio is superior to phenytoin and phenobarbitol (grade C recommendation). Patients should be treated with an optimum dose of carbamazepine at least once in the context of this monotherapy (expert consensus).

The other therapeutic alternatives are gabapentin, lamotrigine and levetiracetam.

Practitioners are advised to turn to bitherapy only after at least two monotherapies have failed. Combinations of more than two anti-epileptic drugs are not recommended.

5.3.2. As part of adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy

The NICE recommendations issued in 2004[4] advise that juvenile myoclonic epilepsy be addressed first with either valproic acid or lamotrigine.

NICE's recommendations for second-line treatment are: clobazam, clonazepam, levetiracetam and topiramate.

The Transparency Committee emphasises that levetiracetam is the only substance to be authorised for the indication "juvenile myoclonic epilepsy". Benzodiazepines are indicated in the treatment of generalised forms of epilepsy (involving absence, myoclonic and tonicoclonic seizures), and topiramate is indicated in the treatment of generalised tonicoclonic epilepsy.

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[2] Consensus-building conference, Treatment of partial drug-resistant epilepsy. Agreed text. March 2004. ANAES, FFN and LFCE.

[3] Référentiel National – Collège des Enseignants de Neurologie. Version of 30/08/2002.

[4] The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE October 2004.

The use of some anti-epileptic drugs can aggravate the symptoms of juvenile myoclonic epilepsy. NICE's recommendations therefore advise against the use of some anti-epileptic drugs in the treatment of this type of epilepsy. They are carbamazepine, oxcarbamazepine, phenytoin, tiagabine and vigabatrin.

5.4. Target populations

- KEPPRA is indicated "As monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over recently diagnosed with epilepsy":

The target population for KEPPRA is estimated from the following data [INSEE, 2006 demographic report; ANAES 2004]:

- Total population aged over 16 as of 1 January 2007: 49,500,000
- Prevalence of epilepsy: 5‰ to 7‰
- Frequency of partial seizures: 60%

The number of patients who could be given KEPPRA in monotherapy as a first-line treatment would therefore be between 149,000 and 208,000.

- KEPPRA is indicated "As part of adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy":

The target population for KEPPRA is estimated from the following data [INSEE, 2006 demographic report; ANAES 2004; EPAR]:

- Total population aged over 12 as of 1 January 2007: 52,500,000
- Prevalence of epilepsy: 5‰ to 7‰
- Frequency of Juvenile Myoclonic Epilepsy: 5% to 10%.
- 10% to 20% of patients require combination anti-epileptic therapy.

The number of patients who could be given KEPPRA as part of combination treatment of juvenile myoclonic epilepsy would therefore be between 1,300 and 7,350.

5.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the marketing authorisation.

5.5.1. Packaging

Appropriate for the prescription conditions.

5.5.2. Reimbursement rate: 65%