HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

10 October 2007

KEPPRA 250 mg, film-coated tablets
Pack of 60 tablets (CIP: 356 013-6)

KEPPRA 500 mg, film-coated tablets
Pack of 60 tablets (CIP: 356 016-5)

KEPPRA 1000 mg, film-coated tablets
Pack of 60 tablets (CIP: 356 022-5)

KEPPRA oral solution 100 mg/ml
One 300-ml bottle (CIP: 370 238-1)

KEPPRA 100 mg/ml, concentrate for solution for infusion
Pack of 10 vials (CIP: 375 893-8)

Applicant: UCB PHARMA SA

levetiracetam
List I
N03AX14
Date of Marketing Authorisation:
KEPPRA 250 mg, 500 mg, 1000 mg film-coated tablets 29/09/2000;
KEPPRA 100 mg/ml oral solution: 03/03/2003
KEPPRA 100 mg/ml, concentrate for solution for infusion 29/03/2006

Date of MA variation:
KEPPRA 250 mg, 500 mg, 1000 mg film-coated tablets and KEPPRA 100 mg/ml oral solution: 13/09/2005 (Extension of indication in children from 4 years).
27/04/2006 (EI in juvenile myoclonic seizures)
07/08/2006 (EI for monotherapy in adults)
04/01/2007 (EI in primary generalised tonic-clonic seizures)

Reason for request:
Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents aged 12 and older with idiopathic generalised epilepsy”.

Health Technology 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 aged 16 and older with newly diagnosed epilepsy.

KEPPRA is indicated **as adjunctive therapy**:

- In the treatment of partial-onset seizures with or without secondary generalisation in adults and children aged 4 and older with epilepsy.
- In the treatment of myoclonic seizures in adults and adolescents aged 12 and older with Juvenile Myoclonic Epilepsy.
- **In the treatment of primary generalised tonic-clonic seizures in adults and adolescents aged 12 and older with Idiopathic Generalised Epilepsy.**

Keppra concentrate for solution for infusion is an alternative for patients when oral administration is temporarily not feasible.

1.3. Dosage

Oral route:
The daily dose is administered in two equally divided doses.
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food.
The oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe and instruction for use in the package leaflet are provided with Keppra.

Monotherapy:
Adults and adolescents age 16 and older:
The recommended starting dose is 250 mg twice daily which should be increased to a 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 upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on therapy:
Adults (≥18 years) and adolescents (12 to 17 years) weighting 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 increases and reductions can be made in 500 mg twice daily increases or decreases every two to four weeks.
Children aged 4 to 11 years and adolescents (12 to 17 years) weighting less than 50 kg:
The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose may be increased up to 30 mg/kg twice daily. Dose increases and reductions 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:

Body 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	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 100 mg/ml oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.
The graduated oral syringe contains up to 1,000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0.25 ml).

Infants and children less than 4 years:
Keppra is not recommended for use in children under 4 years of age due to insufficient data on safety and efficacy.

Elderly (65 years and older):
Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment:
The daily dose must be individualised according to renal function (cf. SPC).

Hepatic impairment:
An adjustment of the dose is recommended in case of severe hepatic insufficiency (cf. SPC).

KEPPRA 100 mg/ml, concentrate for solution for infusion
Conversion to or from oral to intravenous administration can be done directly without controlling plasma levetiracetam levels. Total daily dose and frequency of administration should be maintained.
Keppra concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously over 15-minutes.
There is no available data about administration of intravenous levetiracetam for a longer period than 4 days.

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

Committee Opinion of February 7, 2001

In the indication “adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation”, the actual benefit of KEPPRA is significant.
Given its pharmacokinetic profile and the fact that levetiracetam is well tolerated, KEPPRA doesn’t offer any improvement in actual 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 1,000mg 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.

Committee Opinion of July 19, 2006

The actual benefit offered by these proprietary products is substantial 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 interactions between levetiracetam and the poor availability of third-generation anti-epileptics drugs for children, the oral forms of KEPPRA provides 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 1,000 mg film-coated tablets, offers no improvement in actual benefit (level V) in adults.

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

Committee Opinion of February 28, 2007

In the following extensions of indication: "monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from age 16 and older with newly diagnosed epilepsy" and "as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults and children age 4 and older with epilepsy" the actual benefit of levetiracetam is significant.

Levetiracetam provides a minor improvement in actual benefit (IAB IV) in terms of safety compared to carbamazepine PR in monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients aged 16 and older with newly diagnosed epilepsy.

Levetiracetam provides a moderate improvement in actual benefit (IAB III) in the management of adults and adolescents aged 12 and older with juvenile myoclonic epilepsy.

Approval for 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 new indications and at the posology of the Marketing Authorisation.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2006)

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

3.2. Medicines in the same therapeutic category

Not applicable

3.3. Medicines with a similar therapeutic aim

Antiepileptics indicated as adjunctive therapy in the treatment of generalised tonic-clonic seizures:

- Phenobarbital - GARDENAL 10 mg, 50 mg and 100 mg, tablets and GARDENAL 40 mg/2 ml and 200 mg/4 ml, formulations for injection - ALEPSAL 15 mg, 50 mg, 100 mg and 150 mg, tablets - APAROXAL 100 mg, tablet - KANEURON 5.4% oral solution (for infants, children and adults);
- Carbamazepine - TEGRETOL 100 mg/5 ml, oral suspension, TEGRETOL 200 mg, scored tablet and TEGRETOL PR 200 mg and 400 mg, film-coated tablet (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, oral solution, DEPAKINE CHRONO 500 mg, tablet PR and DEPAKINE 400 mg/4 ml, preparation for IV injection (for infants, children and adults);
- Clonazepam RIVOTRIL 2 mg cross–scored tablets, RIVOTRIL oral solution 2.5 mg/ml (for infants, children and adults);
- Clobazam URBANYL 10 mg scored tablet 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 capsule, EPITOMAX 25 mg, 50 mg, 100 mg and 200 mg tablets (for children > 2 years and adults);
- Lamotrigine - LAMICTAL dispersible 2-mg tablet, LAMICTAL dispersible tablet or tablet for chewing 5 mg, 25 mg, 50 mg, 100 mg, 200 mg (for children > 2 years and adults)

4 ANALYSIS OF AVAILABLE DATA

The company submitted the results of the pivotal MA study:

- Study N 01057 evaluated the efficacy and safety of levetiracetam as adjunctive therapy *versus* placebo in patients aged from 4 to 65 years with idiopathic generalised epilepsy with primary generalised tonic-clonic (PGTC) seizures[1].
- An open-label extension phase of study N01057 is currently in progress (N167). Interim results were provided by the company. They are not discussed in this opinion

Objectives:

The objective of study N01057 was to evaluate the efficacy and safety of levetiracetam *versus* placebo as adjunctive therapy in patients with idiopathic generalised epilepsy with PGTC seizures.

Methodology:

Study N01057 was a randomised, double-blind, placebo-controlled, parallel-group comparative study.

The efficacy and safety of levetiracetam, administered at a dosage of 3,000 mg divided into 2 equal daily doses, or 60 mg/kg/day (in children aged under 16 years and/or with a weight < 50 kg), were evaluated, over a 28-weeks period, in patients with idiopathic generalised epilepsy with PGTC seizures.

Inclusion criteria:

- Patients aged from 4 to 65 years, with body weight > 20 kg;
- Patients treated with one or two antiepileptics;
- Patients with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures uncontrolled by their usual treatment;
- Patients who had at least 3 primary generalised tonic-clonic seizures during the screening phase before randomization;

The study was composed of several phases:

- Baseline phase of 8 weeks: during the last 4 weeks, patients were treated with a placebo single blind; at the end of this phase patients were randomised or not.
- 4-week treatment titration phase up to the optimal dose of 3,000 mg/day.
- 20-week maintenance phase,

The dose could be reduced to 2,000 mg/day during the first week of the maintenance phase.
The treatment phase is defined as the titration phase and the maintenance phase, thus was of a 24 weeks duration.

After 28 weeks of follow-up, patients were able either to stop the study or to be enrolled in follow-up study N167, of 6 weeks duration.

Primary endpoint: percentage reduction of the weekly PGTC seizure frequency between the baseline phase and the treatment phase (24 weeks).

[1] Berkovic SF et al. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. Neurology July 2007 (article in press, accepted on 19 avril 2007).

Secondary efficacy endpoints taken into account in this opinion: percentage of seizure-free patients during the maintenance phase and treatment phase; percentage of responders (at least 50% reduction in seizure frequency between the baseline phase and the treatment phase).

Results:

After the baseline phase, 164 patients were enrolled in the study, 80 in the levetiracetam group and 84 in the placebo group.

During the baseline phase, 50% of patients were treated by one antiepileptic and 44 % were treated by two antiepileptics.

The most frequently combined antiepileptics during the treatment phase were as follows:

- levetiracetam group: valproic acid (53.2%) and lamotrigine (27.8 %);
- placebo group: valproic acid (52.4%) and lamotrigine (27.4 %);

Table 1: Age and age range distribution in the ITT population

Characteristics	Statistics	PBO (N=84)	LEV (N=80)	Total (N=164)
Age (years)				
	Mean (standard deviation)	**30.59 (12.12)**	**26.89 (11.21)**	**28.79 (11.80)**
	Median	**29.05**	**25.39**	**27.09**
	Min-Max	**7.3 – 60.1**	**5.5 – 62.1**	**5.5 – 62.1**
Age range (years)				
< 6	**N (%)**	**0**	**1 (1.3)**	**1 (0.6)**
6 - <12	**N (%)**	**3 (3.6)**	**5 (6.3)**	**8 (4.9)**
12 - <16	**N (%)**	**5 (6.0)**	**3 (3.8)**	**8 (4.9)**
16 - <65	**N (%)**	**76 (90.5)**	**71 (88.8)**	**147 (89.6)**

Tables 2 and 3 present the different types of epilepsy in the patients enrolled in the study:

Table 2: Distribution of the ITT population according to epileptic syndrome

Epileptic Syndrome	PBO (N=84) n (%)	LEV (N=80) n (%)	Total (N=164) n (%)
Localization related - idiopathic	1 (1.2)	0	1 (0.6)
Confirmed	1 (1.2)	0	1 (0.6)
Generalised - Idiopathic - Childhood absence epilepsy	4 (4.8)	3 (3.8)	7 (4.3)
Confirmed	3 (3.6)	2 (2.5)	5 (3.0)
Suspected	1 (1.2)	1 (1.3)	2 (1.2)
Generalised - Idiopathic – Juvenile absence epilepsy	11 (13.1)	8 (10.0)	19 (11.6)
Confirmed	10 (11.9)	8 (10.0)	18 (11.0)
Suspected	1 (1.2)	0	1 (0.6)
Generalised - Idiopathic - Juvenile myoclonic epilepsy			
Confirmed	30 (35.7)	24 (30.0)	54 (32.9)
Suspected	25 (29.8)	20 (25.0)	45 (27.4)
	5 (6.0)	4 (5.0)	9 (5.5)
Generalised - Idiopathic			
Epilepsy with grand mal seizures on awakening	27 (32.1)	22 (27.5)	49 (29.9)
Confirmed	22 (26.2)	20 (25.0)	42 (25.6)
Suspected	5 (6.0)	2 (2.5)	7 (4.3)
Generalised – Idiopathic - Other generalized idiopathic			
epilepsies not defined above	10 (11.9)	18 (22.5)	28 (17.1)
Confirmed	8 (9.5)	14 (17.5)	22 (13.4)
Suspected	2 (2.4)	4 (5.0)	6 (3.7)
Epileptic Syndrome Unknown	2 (2.4)	5 (6.3)	7 (4.3)

Table 3: Classification of epileptic seizures (ITT population)

Type of seizures Subgroup of seizures	**PBO** **(N= 84)** **n (%)**	**LEV** **(N= 80)** **n (%)**	**TOTAL** **(N= 164)** **n (%)**
Partial-onset seizures	2 (2.4)	3 (3.8)	5 (3.0)
Simple partial seizures (I A)	2 (2.4)	3 (3.8)	5 (3.0)
Generalised-onset seizures (II)	84 (100.0)	80 (100.0)	164 (100.0)
Absences seizures (II A1)	47 (56.0)	31 (38.8)	78 (47.6)
Atypical absence seizures (II A 2)	1(1.2)	1 (1.3)	2 (1.2)
Myoclonic seizures (II B)	35 (41.7)	27 (33.8)	62 (37.8)
Clonic seizures (II C)	1 (1.2)	0	1 (0.6)
Tonic seizures (II D)	5 (6.0)	1 (1.3)	6 (3.7)
Tonic-clonic seizures (II E)	84 (100.0)	80 (100.0)	164 (100.0)

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

Table 4: results of study N01057

	LEV	**PBO**
N (ITT)	80	84
Baseline weekly seizures frequency	1.27 (median**:** 0.62)	1.20 (median: 0.62)
Mean weekly seizures frequency during treatment phase	0.61 (median: 1.9)	1.06 (median: 1.97)
Mean percentage reduction in the weekly PGTC seizures frequency (least squares fit method)	56, 5 % (standard deviation: 7.05)	28.2 % (standard deviation: 6.79)
Difference between the 2 groups (LEV – PBO) 95% CI	28.31 % 95% CI [8.97; 47.64]	
Percentage of responders	72.2 %	45.2 %
	p < 0.001	
Percentage of seizure-free patients* during the treatment phase (all types of seizure together)	15.2 %	6.0 %
	p = 0.072	
Percentage of GTCP seizure-free patients* during the treatment phase	24.1 %	7.1 %
	p = 0.004	

*calculated from the patients who finished the study (LEV group: 79: placebo group: 84); patients who stopped the study and who were seizures-free were not considered to be seizure-free.

Primary efficacy endpoint:

The percentage reduction in the weekly PGTC seizure frequency was significantly greater in the levetiracetam group than in the placebo group (56.5% *versus* 28.2%, difference between the 2 groups: 28.3%; 95% CI [8.97; 47.64]; p=0.004).

Secondary efficacy endpoints:

The responder rate was significantly higher in the levetiracetam group than in the placebo group (72.2% *versus* 45.2%, p < 0.001).

There was no difference in the percentage of seizure-free patients (all types of seizure together) during the treatment period between the two groups. This percentage was significantly higher when the analysis only concerned the primary generalised tonic-clonic seizures: 24.1 % *versus* 7.1 % (p = 0.004).

No difference was observed between the two groups in terms of occurrence of myoclonic seizures or absences during the treatment phase in patients who had never had myoclonic seizures or absences previously:

- Myoclonic seizures: 3.8 % in the levetiracetam group (2/53) *versus* 6.3% in the placebo group (3/48) (NS);
- Absence seizures: 14.9 % in the levetiracetam group (7/47) *versus* 5.7% in the placebo group (2/35) (NS);

In the levetiracetam group, 13.8% of patients stopped their treatment (11/80), 2 because of adverse events (aggressiveness, agitation and nervousness), 5 patients were lost to follow-up, and the 4 other patients for other reasons.

In the placebo group, 23.8% of patients stopped their treatment (20/84), 7 because of adverse events (insomnia, depression, agitation), 3 because of lack of efficacy, 1 patient was lost to follow-up, and the 9 other patients dropped out for other reasons.

Safety:
In this study, 72.2% of the patients in the levetiracetam group had an adverse event during treatment *versus* 67.9% of patients in the placebo group. Most of these events were considered to be mild or moderate in severity.
The most common adverse events (> 5 %) were:

	LEV	PBO
Nasopharyngitis	**13.9 %**	**4.8 %**
Fatigue	**10.1 %**	**8.3 %**
Dizziness	**7.6 %**	**9.5 %**
Nausea	**3.8 %**	**8.3 %**
Diarrhoea	**7.6 %**	**7.1 %**
Headache	**10.1 %**	**11.9 %**
Irritability	**6.3 %**	**2.4 %**
Mood disorders	**1.2 %**	**5.1 %**

Adverse events possibly related to treatment were observed in 39.2% of patients in the levetiracetam group *versus* 29.8% of patients in the placebo group.
Among these adverse events, fatigue (10.1% *versus* 6.0%) and psychiatric disorders such as mood disorders (22.8% *versus* 14.3%) were more frequent in the levetiracetam group than in the placebo group.
During the study, one patient died of SUDEP (*SUdden Death in EPilepsy*).

Conclusions:
The analysis of the results of study N 01057 showed the superior efficacy of levetiracetam compared to placebo as adjunctive therapy in the treatment of PGTC seizures in uncontrolled patients with idiopathic generalised epilepsy. The mean percentage reduction in the PGTC seizure frequency between the baseline phase and the treatment phase was significantly greater in the levetiracetam group than in the placebo group (56.5 % *versus* 28.2 %, $p = 0.004$). The responder rate was also significantly higher in the levetiracetam group than in the placebo group (72.2% *versus* 45.2%, $p < 0.001$) and so was the percentage of PGTC seizure-free patients (24.1 % *versus* 7.1 %, $p = 0.004$). The percentage of seizure-free patients (all types of seizure together) was not significantly different between the two groups.

According to EPAR, levetiracetam as adjunctive therapy in the treatment of PGTC seizures in adults and adolescents over age 12 with idiopathic generalised epilepsy, has no effect on the absence seizure incidence, despite the observed difference (in terms of onset of absence seizures) in the two groups (14.9% in the levetiracetam group *versus* 5.7% in the placebo group).
The Transparency Committee underlines the quantity of effect observed in patients in the placebo group.
In terms of safety, the incidence of mood disorders possibly related to levetiracetam should be underlined.

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 drugs come within the scope of preventive treatment.

The efficacy/safety ratio of these products is high in this indication.
These proprietary medicines are second-line treatment in the indication “adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy”.

Alternative medications exist.

> Idiopathic generalised epilepsy is a moderate public health burden. In the indicated population, the burden is low taking into account the relatively small number of patients concerned (patients suffering from uncontrolled primary generalised tonic-clonic seizures) compared to the whole population of patients suffering from idiopathic generalised epilepsy.
> In terms of public health, there is a need for effective and well-tolerated antiepileptic drugs (in particular for pharmacoresistant epilepsy).
> The available data are not sufficient to assess the impact of KEPPRA, used as adjunctive therapy, compared to other antiepileptic combinations on quality of life and epilepsy-related morbidity and mortality.
> Nevertheless, KEPPRA should provide an additional response to an identified public health need.
> Consequently, KEPPRA is expected to benefit public health in this indication. This benefit is low.

The actual benefit of these proprietary drugs is substantial.

5.2. Improvement in actual benefit

Taking into account its efficacy/safety ratio, KEPPRA, used as adjunctive therapy in the management of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy, provides a level IV improvement in actual benefit.

5.3. Therapeutic use[2]

The ILAE (International League Against Epilepsy) system for classification of epilepsy and epileptic syndromes[3] is based on 2 major features:
- Type of seizure: which distinguishes generalised-onset, partial-onset and unclassified seizures.
- Aetiology which distinguishes between idiopathic, symptomatic and cryptogenic epilepsy.

[2] National code of practice – Collège des Enseignants de Neurologie. Version of 30/08/2002.
[3] Commission on classification and terminology of the International League Against Epilepsy. Proposal for revised clinical and EEG classification of epileptic seizures. Epilepsia 1989; 30: 389-399.

There are 5 types of generalised-onset seizure:
- Absence seizures;
- Myoclonic seizures;
- Clonic seizures;
- Tonic seizures;
- Tonic-clonic seizures.

Patients are staged according to their main type of seizure though this does not mean that they cannot subsequently have another type of seizure.

The institution of antiepileptic treatment obeys certain rules. It is essential:

- To be certain of the diagnosis of an epileptic seizure;
- To take measures to avoid precipitating causes;
- To clearly recognise the forms that don't require medication;
- To choose the antiepileptic according to the type of seizure, epileptic syndrome and Marketing Authorisation;
- Always start with monotherapy, with gradual up-titration to the lowest recommended dosage according to age and body weight; in case of failure of a first monotherapy, a second monotherapy may be initiated. Multiple-agent therapy should only be attempted in case of failure of this second monotherapy.

According to the experts, the medication used as adjunctive therapy in patients with primary generalised tonic-clonic seizures must have the broadest action spectrum or, when applicable, not worsen the other seizures types that the patient may subsequently presents. Hence the main difficulty facing neurologists is to identify as precisely as possible the type of epilepsy suffered by the patient.

According to the NICE 2004 guidelines[4], generalised tonic-clonic seizures must be initially managed by valproic acid, carbamazepine, lamotrigine, or topiramate.
Among the active comparators of levetiracetam used as adjunctive therapy in the extension of indication evaluated in this opinion, the French Transparency Committee points out that carbamazepine is not effective against absence and myoclonic seizures which may sometimes be worsened, and that the efficacy of topiramate has not been demonstrated in absence seizures.
In case of lack of efficacy, the second-line medicinal products recommended by NICE are clobazam, oxcarbazepine and levetiracetam (oxcarbazepine is not indicated in the treatment of generalised tonic-clonic seizures).
The symptoms of generalised tonic-clonic seizures may be worsened by the use of certain antiepileptics. According to the NICE guidelines, number of antiepileptics are therefore not recommended in the treatment of these seizures: these include tiagabine and vigabatrin.

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

5.4. Target population

The target population of KEPPRA may be estimated from the following data [INSEE, population census 2006; ANAES 2004; EPAR]:

- The total population aged 12 years or more on 1 January, 2007 was 52,500,000.
- The prevalence of epilepsy is between 5‰ and 7‰. The French population concerned is therefore between 262,500 and 367,500 patients.
- 15 to 20%[5] of these patients have idiopathic generalised epilepsy, i.e. from 39,375 to 73,500 patients.
- Approximately 20% of idiopathic generalised epilepsies are pharmacoresistant (expert opinions).

Consequently, the number of patients liable to receive KEPPRA as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures during idiopathic generalised epilepsy is between 8,000 and 15,000.

5.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion of KEPPRA 250 mg, 500 mg and 1000 mg film-coated tablets and KEPPRA 100 mg/ml oral solution 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 new indication and at the posology of the Marketing Authorisation.

The Transparency Committee recommends inclusion of KEPPRA 100 mg/ml concentrate for dilution for infusion on the list of medicinal products approved for use in the hospital sector and various public departments in the new indication and at the posology of the Marketing Authorisation.

5.5.1. Packaging:

Appropriate to the conditions of prescription

5.5.2. Reimbursement rate: 65 %

[5] Jallon P et al. Epidemiology of idiopathic generalized epilepsies. Epilepsia, novembre 2005(vol. 46), suppl 9: 10-14.