TRANSPARENCY COMMITTEE

OPINION

22 September 2010

ZEBINIX 800 mg, tablet
B/30 (CIP code: 397 349-9)

Applicant: EISAI SAS

eslicarbazepine acetate
ATC code: N03AF04

List I

Date of Marketing Authorisation (centralised procedure): 21 April 2009

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
eslicarbazepine acetate

1.2. Indication
“ZEBINIX is indicated as adjunctive therapy in adults with partial-onset epilepsy with or without secondary generalisation.”

1.3. Dosage
“ZEBINIX must be added to existing anti-epileptic therapy. The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1200 mg once daily.

ZEBINIX may be taken with or without food.

Elderly (over 65 years of age)
Particular caution should be exercised in the treatment of elderly patients as there is limited tolerance information on the use of ZEBINIX in these patients.

Paediatric population
ZEBINIX is not recommended for use in children below 18 years as there is limited tolerance and efficacy information.

Patients with renal impairment
Caution should be exercised in the treatment of patients with renal impairment and the dosage should be adjusted according to creatinine clearance (CL\textsubscript{CR}) as follows:
- CL\textsubscript{CR} >60 ml/min: no dose adjustment required
- CL\textsubscript{CR} 30-60 ml/min: initial dose of 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- CL\textsubscript{CR} <30 ml/min: use of the product is not recommended in patients with severe renal impairment due to insufficient data.

Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment. The pharmacokinetics of eslicarbazepine has not been evaluated in patients with severe hepatic impairment and use in these patients is therefore not recommended.”
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)
N : Nervous system
N03 : Antiepileptics
N03A : Antiepileptics
N03AF : Carboxamide derivatives
N03AF04 : eslicarbazepine

2.2. Medicines in the same therapeutic category
Other carboxamide derivatives:
- TEGRETOL (carbamazepine) indicated in the treatment of partial-onset epilepsy with or without secondary generalisation and the treatment of generalised seizures: tonic-clonic seizures, as monotherapy or in combination with another antiepileptic therapy in adults and children aged 6 years or over.
- TRILEPTAL (oxcarbazepine) indicated in the treatment of partial-onset epileptic seizures with or without secondary generalisation, as monotherapy or in combination with another antiepileptic therapy in adults and in children aged 6 years or over.

2.3. Medicines with a similar therapeutic aim
These are all the other antiepileptic medicinal products.

2.3.1. Medicines indicated “as adjunctive therapy in the treatment of partial-onset seizures”:
- VIMPAT (lacosamide) in patients aged 16 years or over
- ZONEGRAN (zonisamide) in adult patients
- LYRICA (pregabalin) in adult patients
- GABITRIL (tiagabine) in patients aged 12 years or over
- SABRIL (vigabatrin) indicated only when other appropriate combination therapies have proved inadequate or to be poorly tolerated.

2.3.2. Medicines indicated in the treatment of “partial-onset seizures”, as adjunctive therapy and as monotherapy:
Oral
- 1st generation antiepileptic medicinal products
DIHYDAN (phenytoin)
GARDENAL (phenobarbital)
MYSOLINE (primidone)
- 2nd generation antiepileptic medicinal products
DEPAKINE (sodium valproate)
- 3rd generation antiepileptic medicinal products
EPITOMAX (topiramate)
KEPPRA (levetiracetam)
LAMICTAL (lamotrigine)
NEURONTIN (gabapentin)
Parenteral
DEPAKINE injectable (valproic acid)
DILANTIN (phenytoin)
PRO-DILANTIN (fosphenytoin)
GARDENAL (phenobarbital)
KEPPRA (levetiracetam)
3. ANALYSIS OF AVAILABLE DATA

The clinical development of eslicarbazepine (ZEBINIX) is based mainly on 3 pivotal studies with the same objectives and the same methodology (studies BIA-2093-301, BIA-2093-302, and BIA-2093-303). These studies involved a one-year open follow-up. The results for efficacy and tolerance (the primary objective of this extension phase) will be described for information purposes, these results being of an exploratory nature.

3.1. Efficacy results

Aim and method:
The main aim of the phase III, randomised, double-blind, placebo-controlled studies BIA-2093-301, BIA-2093-302, and BIA-2093-303 was to evaluate the efficacy and tolerance of 3 doses of ZEBINIX (400 mg, 800 mg and 1200 mg) administered in combination with 1 or 3 antiepileptic medicinal products in a total of 1050 patients with refractory partial-onset epileptic seizures with or without secondary generalisation who were followed up for 12 weeks.

Note: Three dosages of eslicarbazepine were evaluated in these phase III studies: 400, 800 and 1200 mg. Marketing Authorisation was granted for dosages of 400, 600, and 800 mg, but the company seeks inclusion for the 800 mg dosage only. Only the results observed for this dosage will be presented. A method for controlling alpha inflation due to multiple comparisons was used for evaluating the efficacy endpoints and avoiding overestimation of the effect observed.

These studies comprised 2 periods:
- a treatment period of 14 or 18 weeks (depending on the study) consisting of 3 or 4 phases:
  - an 8-week inclusion phase
  - a 2-week titration phase
  - a 12-week treatment “maintenance” phase, during which the treatment was evaluated
  - a 4-week tapering-off phase in which the dose was reduced (studies BIA-2093-301 and BIA-2093-303 only)
- a 1-year open-label follow-up.

From the titration phase, these studies included 1049 patients in total, 289 in the placebo groups and 760 in the ZEBINIX treatment groups, 284 of the latter being treated with ZEBINIX 800 mg. The ITT population included 286 patients in the placebo groups and 282 patients in the ZEBINIX 800 mg group.

The protocol planned a pooled analysis of the results of the 3 studies.

3 Defined by the set of randomised patients who received the treatment at least once and for whom an evaluation of seizure frequency is available
Inclusion criteria: patients aged 18 years or over:
- with simple (accompanied by motor signs) or complex partial-onset seizures with or without secondary generalisation for at least 12 months,
- with at least 4 partial-onset seizures in each 28-day period during the 8 weeks leading up to inclusion,
- receiving antiepileptic medicinal products (≤ 2 in studies 301 and 303 and ≤3 in study 302) in a stable regimen for at least 2 months.

Non-inclusion criteria:
- Only simple partial-onset epileptic seizures with no motor symptoms (no EEG),
- Primary generalised epilepsy,
- Rapidly progressive neurological disorders,
- History of status epilepticus or cluster seizures (3 or more seizures in 30 minutes) in the 3 months leading up to inclusion,
- Epileptic seizures of psychogenic origin during the last two years,
- Patients treated with oxcarbazepine or felbamate.

Primary efficacy endpoint:
Seizure frequency in the 12-week treatment “maintenance” period, standardised to a frequency per 4 weeks.

Main secondary endpoints:
- Responder rate, defined as the percentage of patients with an at least 50% reduction in seizure frequency after 12 weeks of treatment (maintenance phase compared to inclusion),
- Number of days with seizures,
- Evaluation of quality of life (clinical global evaluation scale - CGI, QUOLIE-31 questionnaire),
- Depressive symptoms (MADRS scale).

Results:

Table 1: Demographic and clinical characteristics of the patients on inclusion

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 289)</th>
<th>ZEBINIX 800 mg group (n = 284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36.9 ± 12.01</td>
<td>38.0 ± 11.96</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.7 ± 13.1</td>
<td>22.6 ± 12.3</td>
</tr>
<tr>
<td>Mean age at diagnosis ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.1 ± 12.3</td>
<td>15.4 ± 13.4</td>
</tr>
<tr>
<td>Possible aetiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>104 (36.0%)</td>
<td>113 (39.8%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>78 (27.0%)</td>
<td>64 (22.5%)</td>
</tr>
<tr>
<td>Head injury</td>
<td>39 (13.5%)</td>
<td>33 (11.6%)</td>
</tr>
<tr>
<td>Congenital/hereditary</td>
<td>25 (8.7%)</td>
<td>26 (9.2%)</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>22 (7.6%)</td>
<td>29 (10.2%)</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>12 (4.2%)</td>
<td>9 (3.2%)</td>
</tr>
<tr>
<td>Systemic/toxic/metabolic</td>
<td>4 (1.4%)</td>
<td>3 (1.1%)</td>
</tr>
</tbody>
</table>

4 Defined according to the international classification of partial-onset epilepsy of 1981
5 CGI = Clinical Global Impression. A 7-point scale that evaluates the overall improvement in the patient due to treatment. The ratings run from 0 (improvement not evaluated) to 7 (patient very much worse).
6 QUOLIE-31 = Quality of life in epilepsy inventory-31. A quality-of-life scale consisting of 7 subscales evaluating emotional well-being, social function, physical capacity, cognitive functions, fear of seizures, the effect of treatment, and overall quality of life.
7 MADRS = Montgomery and Asberg Depression Rating Scale. A scale yielding a score of 0 to 60 which evaluates the effect of treatment on the severity of depression in very different areas such as mood, sleep, appetite, physical and psychological lassitude, and suicidal thoughts.
The characteristics of the patients in each group were comparable on inclusion.

On average, the patients were about 37 years of age, the epilepsy had started in adolescence, had on average been present for more than 22 years, and was in most instances idiopathic or of unknown origin.

At the time of inclusion, the mean frequency of seizure was approximately 13 per 4 weeks in all the treatment groups (12.9 in the placebo group and 13.4 in the ZEBINIX 800 mg group).

Roughly 70% of the patients used 2 concomitant antiepileptic medicinal products, the ones used most being carbamazepine, valproic acid, and lamotrigine.

**Primary endpoint:**

1. *Results of the individual studies*

<table>
<thead>
<tr>
<th>Study 301</th>
<th>Study 302</th>
<th>Study 303</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo group n = 102</td>
<td>ZEBINIX 800 mg group n = 98</td>
</tr>
<tr>
<td>Number of patients evaluated</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>Mean seizure frequency, 95% CI</td>
<td>7.6 [6.8; 8.6]</td>
<td>5.7 [5.0; 6.5]</td>
</tr>
<tr>
<td>Mean difference versus placebo (p)</td>
<td>-1.9 p = 0.003</td>
<td>-2.7 p = 0.002</td>
</tr>
</tbody>
</table>

After 12 weeks of treatment, a statistically significant decrease in the number of seizures per 4-week period was observed in the ZEBINIX 800 mg group compared to placebo in each of the studies.

These results were confirmed in the pooled analysis (p < 0.001).
2. Results of the pooled analysis

Table 3: Pooled analysis of seizure frequency per 4-week period during the 12-week treatment maintenance phase (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Placebo group n = 286</th>
<th>ZEBINIX 800 mg group n = 282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of seizures on inclusion ± SD</td>
<td>12.9 ± 16.8</td>
<td>13.4 ± 15.3</td>
</tr>
<tr>
<td>Mean number of seizures during the maintenance phase ± SD</td>
<td>11.7 ± 17.9</td>
<td>9.8 ± 14.8</td>
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</table>

3. Results of the follow-up at 1 year

The data from this follow-up are presented for information purposes. No conclusion can be drawn from this type of descriptive analysis.

The analysis involved 828 patients (312 in study 301, 325 in study 302, and 191 in study 303). The mean administered dose of eslicarbazepine was 893 ± 234 mg in study 301, 890 ± 192 mg in study 302, and 917 ± 179 mg in study 303.

After 1 year of treatment, the mean decrease in the number of seizures per 4-week period compared to baseline (mean number of seizures: 13.4) was 4.8 in studies 301 and 302 and 5.4 in study 303.

Secondary endpoints:

- Responder rate
  In the pooled analysis of the results of the 3 studies, the responder rate was 36.3% in the ZEBINIX group and 21.5% in the placebo group (RR = 1.69 95% CI [1.28; 2.22], p < 0.001).

  Looking at the studies individually, this rate was:
  - 35.1% in the ZEBINIX 800 mg group and 20.2% in the placebo group in study 301 (p = 0.02),
  - 37.5% in the ZEBINIX 800 mg group and 18.2% in the placebo group in study 302 (p = 0.003),
  - 36.3% in the ZEBINIX 800 mg group and 27.2% in the placebo group in study 303 (NS).

- Number of days with seizures
  In the pooled analysis of the studies, in the ITT population, the mean number of days with seizures per 4-week period at the time of inclusion was 8.0 ± 5.7 in the patients in the placebo group and 8.5 ± 5.8 in the patients in the ZEBINIX group.

  After 12 weeks of treatment, the mean number of days with seizures per 4-week period was 7.0 ± 5.8 in the placebo group (n = 279) and 6.1 ± 5.8 in the ZEBINIX group (n = 262), p = 0.0054.

- Quality of life
  No difference was seen on the various evaluation scales.
3.2. Adverse Effects

Adverse events were reported in 46.4% of the patients in the placebo group (134/289) and 62.7% of the patients in the ZEBINIX 800 mg group (178/284). These adverse events were possibly connected with the treatment in 24.9% of the patients in the placebo group and 47.2% of the patients in the ZEBINIX group.

The main adverse events were:
- dizziness, occurring in 60/284 patients receiving ZEBINIX versus 21/289 patients in the placebo group
- drowsiness, occurring in 37/284 patients receiving ZEBINIX versus 27/289 patients in the placebo group
- headache, occurring in 29/284 patients receiving ZEBINIX versus 25/289 patients in the placebo group
- nausea, occurring in 21/284 patients receiving ZEBINIX versus 6/289 patients in the placebo group
- vomiting, occurring in 19/284 patients receiving ZEBINIX versus 7/289 patients in the placebo group

The number of patients who discontinued treatment on account of adverse events was 13 in the placebo group and 33 in the ZEBINIX group.

The patients included in the open-label follow-up phase (312 in study 301, 325 in study 302, and 194 in study 303) received ZEBINIX at a dosage of 800 mg. After 1 year of treatment, the proportion of patients who had experienced adverse events possibly connected with the treatment was 51% in study 301, 83% in study 302, and 58% in study 303. The main adverse events observed were dizziness (10.2% of the patients in study 301, 27% in study 302, 17% in study 303), drowsiness (12% in study 302, 10% in study 303) and headaches (10.2% in study 301, 16% in study 303).

3.3. Conclusion

The efficacy and tolerance of 3 dosages of ZEBINIX (400, 800, and 1200 mg eslicarbazepine acetate) were evaluated in three phase III, randomised, double-blind, placebo-controlled studies in 1049 adult patients with partial-onset epilepsy refractory to treatment combining one to three antiepileptic medicinal products. The results presented are those for the ZEBINIX 800 mg group (the only dosage for which inclusion is sought).

After 12 weeks’ treatment, a statistically significant decrease in the number of seizures per 4-week period was observed in the ZEBINIX 800 mg group compared to placebo in each of the studies (a decrease of 1.6, 1.9, and 2.7 seizures, depending on the study). In the pooled analysis of these results specified by the protocol, a statistically significant decrease in seizure frequency was found between the placebo group and the ZEBINIX 800 mg group (mean difference of 2 in the number of seizures between the groups, p < 0.0001). In the pooled analysis, the responder rate was 36.3% in the ZEBINIX group and 21.5% in the placebo group (RR = 1.69 95% CI [1.28; 2.22], p < 0.001).

No difference was seen on the various quality-of-life scales evaluated.

The main events observed were ones of a gastrointestinal nature and nervous system disorders. No rare adverse effects, such as bone-marrow aplasia, anaphylactic reactions, severe skin reactions (such as Stevens-Johnson syndrome), disseminated lupus erythematosus or severe cardiac arrhythmia, were observed in the placebo-controlled studies. They have, however, been reported with oxcarbazepine. Their occurrence following ZEBINIX therapy is
thus not ruled out, as these 2 active ingredients are pharmacologically similar. Skin reactions are one of the risks that are to be monitored in the RMP. It is regrettable that comparative studies versus other antiepileptic therapies indicated in combination in the management of partial-onset epilepsy with or without secondary generalisation are not available for assessing the true benefit afforded by ZEBINIX. The efficacy of ZEBINIX seems to be of the same order as that of the main comparators in terms of the number of seizures per 4-week period8.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
Epilepsy is a serious disease. Epileptic seizures are symptoms of a highly heterogeneous array of disorders. Epilepsy, characterised by the – usually spontaneous – recurrence of these seizures over the medium and long term, can markedly impair patients' quality of life. ZEBINIX is a symptomatic treatment which is indicated in combination with other antiepileptic medicinal products in the treatment of partial-onset epileptic seizures with or without secondary generalisation in adults. The efficacy/adverse effects ratio of ZEBINIX is high. Numerous alternative medicinal products exist.

**Public health benefit:**
Partial-onset epilepsy is a common disease, and the recurrence of the seizures in some patients can markedly impair their quality of life and can cause substantial disability with consequences for family life, work life, and social integration. Overall, partial-onset epilepsy represents a moderate public health burden. The burden in respect of the population of patients suffering from partial-onset epilepsy after failure of monotherapy is also considered to be moderate. Preventing disabilities associated with epilepsy and their consequences, a task in which ZEBINIX could be of assistance, is a public health objective that is an established priority (Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives], DGS - 2003). This need remains in so far as drug-resistant partial-onset epilepsy is still common and is the cause of considerable disability.

In the absence of data versus an active comparator and in view of the limited data on the continuation of treatment and tolerance in the long term, a hoped-for additional impact on the morbidity of patients treated with ZEBINIX, used in combination, in this indication cannot be assumed. Furthermore, it is not possible, on the basis of the available data, to evaluate the impact of ZEBINIX on the quality of life of the patients treated. The impact of the treatment on other parameters such as disability, work life, and social integration is not documented. No impact on the organisation of the healthcare system is expected. It is thus not possible to know whether ZEBINIX, in this indication, will be able to make an additional contribution towards meeting the identified public-health need.

Consequently, in the current state of knowledge and in view of the fact that other therapies are already available, it is not expected that ZEBINIX will benefit public health in this indication.

The actual benefit of ZEBINIX is substantial.

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8 The size of the difference in the standardised frequency of seizures versus placebo was:
- 26 to 50% for the TRILEPTAL proprietary medicinal products (depending on the dosage) and the LYRICA proprietary medicinal products (cf opinion of 16 March 2005)
- 21 to 29% for the ZONEGRAN proprietary medicinal products (cf TC opinion of 16 November 2005)
- 15 to 28% for the VIMPAT proprietary medicinal products (cf opinion of 4 March 2009)
- 20 to 30% for ZEBINIX 800 mg.
4.2. Improvement in actual benefit (IAB)

In view of the absence of comparative data from other antiepileptic medicinal products and of the results observed in the studies, the transparency Committee considers that ZEBINIX, used in combination with other antiepileptic medicinal products, does not provide an improvement in actual benefit (IAB V) in the management of adult patients with partial-onset epilepsy with or without secondary generalisation.

4.3. Therapeutic use

The antiepileptic treatment chosen depends on the characteristics of the epileptic syndrome and the specifics of the patient.

In the management of newly or recently diagnosed partial-onset epilepsy, monotherapy is the recommended first-line approach, using, in particular, carbamazepine or valproic acid on account of their superior risk/benefit ratio in comparison with phenytoin and phenobarbital (recommendation level C). Optimal-dose carbamazepine therapy must be used at least once in such monotherapy (expert consensus). The other treatment alternatives are gabapentin, lamotrigine, and levetiracetam.

In the event of failure (inadequate response, adverse effects resulting in discontinuation of treatment) in spite of an adequate dosage and adequate compliance with the treatment, replacement monotherapy is gradually introduced. At least two different monotherapies must be attempted. In the treatment of partial-onset epileptic seizures, carbamazepine and sodium valproate are the standard therapies. Oxcarbazepine, lamotrigine, and gabapentin are indicated as first-line monotherapy or in combination. Since these recommendations, levetiracetam has also been granted Marketing Authorisation (2005) as first-line monotherapy.

The use of a combination of more than 2 antiepileptic medicines is not recommended (Level C).

Addition of a second antiepileptic medicinal product is recommended if the response to the preceding monotherapies is insufficient. ZEBINIX is a new therapeutic tool that supplements existing treatments.

The effect of ZEBINIX on primary generalised epilepsy has not been investigated. Its use in this type of patient is thus not recommended.

4.4. Target population

The target population of ZEBINIX is patients aged 18 years or over with partial-onset epileptic seizures with or without secondary generalisation requiring treatment with a combination of antiepileptic medicinal products.

It can be estimated from the following data:
- The number of epileptic patients in France is estimated to be between 350,000 and 400,000.\(^7\)\(^,\)\(^10\)
- Partial-onset seizures account for approximately 60% of all epileptic seizures\(^7\)\(^,\)\(^11\), i.e. 210,000 to 240,000 patients;

- Monotherapy is effective in approximately 70 to 80% of cases; thus 20 to 30% of patients may receive ZEBINIX in combination with other antiepileptic medicinal products. The target population of ZEBINIX can be estimated at between 42,000 and 72,000 patients. It should be noted that the data on the use of ZEBINIX in persons over 65 years of age are insufficient.

4.5. Transparency Committee recommendations
The transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%