

**rufinamide 100mg, 200mg and 400mg tablets
(Inovelon®)**

No. (416/07)

Eisai Limited

5 October 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rufinamide (Inovelon®) is not recommended for use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients four years and older.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients four years and older.

Dosing information

Children ≥ 4 years and <30 kg

Patients <30 kg not receiving valproate:

Initially 200 mg daily. Dose may be increased according to clinical response by 200 mg/day, every two days, up to a maximum recommended dose of 1000 mg/day.

Children ≥ 4 years and <30 kg also receiving valproate:

Initially 200 mg daily. After a minimum of 2 days the dose may be increased according to clinical response by 200 mg/day, to the maximum recommended dose of 400 mg/day.

Adults and children ≥ 4 years and ≥ 30 kg:

Initially 400 mg daily. Dose may be increased according to clinical response by 400 mg/day, every two days, up to a maximum recommended daily dose of 1800-3200 mg depending on body weight.

Product availability date

24 September 2007. This product has Orphan drug status.

Summary of evidence on comparative efficacy

Rufinamide is a triazole derivative structurally unrelated to other currently available antiepileptic drugs (AEDs). The principal mechanism of action is considered to be the modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel.

The Lennox-Gastaut syndrome (LGS) is rare and one of the most severe forms of epilepsy, usually affecting children between 1 and 8 years (typically between 3 and 5 years) but occasionally has its onset in children who are more than 8 years old. It continues into adulthood in a large number of patients. LGS is characterised by three clinical features; multiple seizure types, generalized discharges with slow spike-and-wave complexes in the electroencephalogram (EEG) and interference with all aspects of the child's intellectual and social development.

One placebo-controlled double-blind trial has been conducted to evaluate rufinamide as adjunctive therapy in patients with LGS. An open-label extension phase of this trial evaluated long-term treatment with rufinamide in LGS. The double-blind trial recruited 139 patients between 4 and 30 years of age with 90 or more seizures in the month prior to baseline including atypical absence seizures and tonic-atonic seizures (commonly referred to as drop attacks). Patients must have been treated with up to 3 fixed-dose concomitant AEDs at study entry, weighed at least 18kg and had an EEG within the previous 6 months demonstrating a slow spike-and-wave pattern. Following a 28-day baseline phase, during which patients' individual seizure type and frequency were assessed, 138 patients were randomised equally to rufinamide or placebo in addition to their standard AED regimens and entered a 12-week double-blind phase.

During the two-week titration phase, rufinamide started at 10mg/kg/day and titrated based on the patient's weight up to a maximum maintenance dose of 45 mg/kg/day administered in 2 divided doses. The dose at the end of the titration period continued as a fixed dose throughout the 10-week maintenance period.

The primary efficacy variables in the intention-to-treat population were percentage changes versus baseline in the frequency per 28 days of (1) total seizures, (2) tonic-atonic seizures and (3) the change in seizure severity according to a 7-point Global Evaluation of the patient's condition at the end of the double-blind phase. The trial was completed by 123 patients. The median percentage change in seizure frequency during the double-blind phase was significantly greater with rufinamide compared to placebo for total seizures (-33% from a baseline of 290 per 28 days vs. -12% from a baseline of 205) and for tonic-atonic seizures (-43% from a baseline of 92 per 28 days vs. +1.4% from a baseline of 93). The patient/carer Global Evaluation showed a significant improvement in seizure severity at the end of the double-blind phase in the rufinamide compared with the placebo group (53% vs. 31%). In addition, the overall response rate was significantly higher in the rufinamide group: 31% of patients had a total seizure frequency reduction of $\geq 50\%$, compared with 11% in the placebo group. For tonic-atonic seizures a $\geq 50\%$ reduction in seizure frequency was achieved by 43% of patients in the rufinamide group and 17% receiving placebo.

An open-label extension study of up to 36-months included 123 patients (63 and 60 rufinamide and placebo-treated patients respectively) who were previously recruited to the first study plus one patient who directly entered the extension phase. The extension phase consisted of a 14-day double-blind conversion period (where placebo-treated patients were titrated up to a maximum maintenance rufinamide dose of 45 mg/kg/day) and an open-label period. Rufinamide treated patients remained on the same dose. The protocol did not define any efficacy variables for the extension phase. Efficacy variables identified by the company after the study was completed included the percentage change in seizure frequency (total and tonic-atonic) per 28 days relative to baseline determined for 2 cohorts: patients who had received rufinamide during both the double-blind phase and the extension phase, and patients who had received placebo during the double-blind phase and rufinamide during the extension phase. Sixty-seven percent (83/124) of patients received rufinamide for ≥ 1 year, 60% (74/124) for ≥ 18 months and 41% (51/124) for ≥ 2 years. The trial was completed by 42 patients. Patients who received rufinamide in both phases continued to experience clinical improvement in total and tonic-atonic seizure frequency and overall response rate. Patients who received placebo during the double-blind phase showed rapid improvement during the first months of open-label treatment with rufinamide and in subsequent months achieved reductions in total and tonic-atonic seizure frequency comparable to those for patients in the original rufinamide group. Overall, the median percent reduction in total seizure frequency per 28 days was 55%, 69% and 79% from baseline at 12, 24 and 36 months respectively, while the median percent reduction in tonic-atonic seizure frequency was 58%, 75% and 76% from baseline at the same time points.

Summary of evidence on comparative safety

In the first study, rufinamide was well tolerated with adverse events (AEs) reported by 81% of patients in both the rufinamide and placebo groups. The most common AEs were somnolence, vomiting, pyrexia, and diarrhoea.

During the open-label extension phase, 91% of patients reported at least one AE; the most frequent were vomiting (31%), pyrexia (26%), upper respiratory tract infection (22%) and somnolence (21%). Decreased appetite and anorexia occurred in 15% and 13% of patients respectively.

Other data were also assessed but remain commercially confidential.*

Summary of clinical effectiveness issues

There are no comparative studies of rufinamide versus topiramate or lamotrigine, both licensed as adjunctive treatment in LGS. In the trials valproate, lamotrigine and topiramate were the most frequently used concomitant AEDs for both rufinamide and placebo treated patients and most patients had two concomitant AEDs.

The European Public Assessment Report (EPAR) noted that it was not possible to determine whether there is development of tolerance to the anticonvulsant effect of rufinamide during long-term treatment. The summary of product characteristics (SPC) states that uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than 3 months.

The EPAR highlights some remaining safety issues. The Committee for Medicinal Products for Human Use (CHMP) has accepted a risk management plan proposing further investigations including monitoring of status epilepticus, hypersensitivity reactions, decreased appetite and weight loss. In addition, the SPC warns that all patients who develop a rash must be closely monitored as serious antiepileptic hypersensitivity syndrome has occurred in association with rufinamide.

Rufinamide concentrations may be affected by other AEDs; the dose may need to be adjusted if changes are made to concurrent AED therapy. Rufinamide doses can be titrated every two days whereas other agents licensed for LGS require dose titration every one to two weeks.

Summary of comparative health economic evidence

The manufacturer submitted a cost-effectiveness analysis using a decision tree model, over a 3-year time horizon and with 3-month cycles. Patients started the model with the baseline seizure frequency observed in the rufinamide trial and commenced adjunctive treatment with rufinamide, lamotrigine, topiramate or a combination of other drugs. After an initial 3-month period, patients entered a maintenance period. Success was defined as a >50% reduction in total or tonic-atonic seizure frequency.

The relative clinical efficacy for the initial 3-month period was derived from the pivotal clinical trials for rufinamide, lamotrigine and topiramate. The outcome measure adopted was the proportion of patients successfully treated with a $\geq 50\%$ reduction in seizure frequency. This was a secondary efficacy variable in the rufinamide trial.

After the initial 3-month period the efficacy rates for the 3 comparators were based on the rufinamide open-label extension study. Resource use was assessed by 5 clinicians using a questionnaire. No utility values were used. The submission noted that published utility values for children with epilepsy and learning difficulties were deemed inappropriate.

The submission expressed the results as the incremental cost per % of patients who achieved a >50% reduction in tonic-atonic and total seizures. Costs for all arms were similar. The incremental cost per % of patients successfully treated was £62 for rufinamide compared to topiramate and £2 compared to lamotrigine using tonic-atonic seizure as the outcome. Rufinamide dominated standard care, being more effective and cheaper. The average number of tonic-atonic seizures per patient treated over three years with rufinamide was 467, 22 (4%) fewer than treatment with topiramate and 26 (5%) fewer than with lamotrigine.

For total seizures, the incremental cost per % of patients successful treated was £434 for rufinamide compared to topiramate, £345 compared to lamotrigine and £85 compared to placebo. The average number of total seizures per patient treated over 3 years with rufinamide was 842, 23 (3%) fewer than with topiramate and 25 (3%) fewer than with lamotrigine.

The main strengths of the analyses were that the model was probabilistic and used appropriate comparators. It was populated with clinical data for the initial 3-month period from 3 relevant trials and the methodology used to calculate relative effects was robust. Resource use and valuation methods were valid.

The main weaknesses of the analysis include:

- The clinical data are from trials that include patients on up to 3 drugs at baseline before adding in the active arm (i.e. fourth line therapy) but the model structure assumes results apply to second-line adjunctive therapy. Clinical use is more likely to be consistent with the use of the drugs in the trials rather than the structure assumed in the model.
- The long-term data are limited and so of questionable value as evidence of long-term efficacy of rufinamide. These data are applied to all 3 arms but may not represent long term effectiveness of the other drugs.
- The effectiveness measure used in the submission, of cost per additional % of patients responding, with at least a 50% improvement in seizure rate, is difficult to use for decision making purposes. The implications for a patient's quality of life or use of resources are not clear.
- Drug costs are not representative of costs to purchase doses but rather are estimated on a lowest price per mg basis. This introduces a bias in favour of rufinamide.

The base-case results show that the drug costs slightly more than its comparators and is marginally more clinically effective as measured by seizures avoided. Sensitivity analyses tend to favour the use of rufinamide with some scenarios reporting it to be more effective and less costly than the alternatives for use in tonic-atonic seizures. However, the modelling and clinical data are not sufficiently robust to inform decisions.

In conclusion, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Epilepsy Scotland

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN): Diagnosis and management of epilepsies in children and young people. A National Clinical Guideline, No 81, published March 2005. SIGN recommends that children with epilepsy should be assessed by a paediatric neurologist or paediatrician with expertise in childhood epilepsy for correct diagnosis. The guideline states that lamotrigine and topiramate are effective add-on treatments in LGS.

National Institute for Health and Clinical Excellence (NICE) guideline; The Epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care; Clinical Guideline No. 20, published October 2004.

NICE Technology Appraisal Guidance No.79, Newer Drugs for Epilepsy in Children, published April 2004.

Both NICE publications indicate that lamotrigine and topiramate should be used as first choice in LGS.

The Cochrane Collaboration; Treatment of Lennox-Gastaut Syndrome (Review), published March 2003, concludes that the optimum treatment for Lennox-Gastaut syndrome remains uncertain and no study to date has shown any one drug to be highly efficacious; lamotrigine, topiramate and felbamate (not licenced in the UK) may be helpful as add-on therapy.

Additional information: comparators

Both lamotrigine and topiramate are indicated as add-on/adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut Syndrome.

Cost of relevant comparators

Drug	Adjunctive Therapy Dose regimen	Cost per year (£)
rufinamide	In patients \geq 4years of 30-50kg after titration up to 1800mg/day orally	2707
topiramate	In children 2-16 years after titration up to 9 mg/kg/day orally*	1155
lamotrigine	In adults and children over 12 years; with valproate regardless of any concomitant medications or without valproate and without inducers or inhibitors of lamotrigine glucuronidation, 100 – 200 mg/day orally	63-125
	without valproate but with other inducers of lamotrigine glucuronidation, 200 – 400 mg/day orally	125-251

Doses are for general comparison and do not imply therapeutic equivalence. Costs for lamotrigine and topiramate are from eVadis on 03/08/07. Costs for rufinamide are from the manufacturer. Costs calculated using the mean age of 14 years and mean weight of 40kg from the baseline characteristics of the pivotal trial. *Cost for nearest dose of 350mg calculated using whole tablets instead of 360mg.

Additional information: budget impact

The manufacturer estimated gross drug costs of £28k in year one rising to £148k in year five. However, after taking account of the costs of other treatments, seizures and adverse events, the net cost was estimated at £9k in year one and £46k in year five. It should be noted that these figures also take account of some personal social services costs, not just NHS costs.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 26 September 2007

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk>