All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Rufinamide (Inovelon®▼) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS)

Eisai Ltd.

Advice No: 1708 – October 2008
Update to FAR –February 2013

Recommendation of AWMSG

Rufinamide (Inovelon®▼) is recommended for use within NHS Wales as an adjunctive therapy in patients four years and older with Lennox-Gastaut syndrome in patients where other adjunctive treatments have proved sub-optimal or have not been tolerated.

Additional note:
AWMSG is of the opinion that rufinamide (Inovelon®▼) tablets for the stated indication may be appropriate for use within NHS Wales prescribed under specialist recommendation.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 15th October 2008

The recommendation of AWMSG is:

Rufinamide (Inovelon®▼) is recommended for use within NHS Wales as an adjunctive therapy in patients four years and older with Lennox-Gastaut syndrome in patients where other adjunctive treatments have proved sub-optimal or have not been tolerated.

Additional notes:

- Rufinamide (Inovelon®▼) may be appropriate for use within NHS Wales prescribed under specialist recommendation.
- AWMSG did not consider that Rufinamide (Inovelon®▼) satisfies their criteria for ultra orphan drug status.

2.0 PRODUCT DETAILS

2.1 Licensed indication
Rufinamide (Inovelon®▼) is licensed as an adjunctive therapy in patients four years and older with Lennox-Gastaut syndrome (LGS)[1].

2.2 Dosing
Rufinamide should be taken orally twice daily with water, in the morning and in the evening, in two equally divided doses. It is preferable to administer the drug with food and if the patient has difficulty with swallowing, the tablets can be crushed[1].

Treatment should be initiated by a physician specialised in paediatrics or neurology with experience in the treatment of epilepsy[1].

Further information regarding specific dosing regimens (based on the weight of the patient) can be found in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date
16th January 2007[2]

2.4 UK Launch date
24th September 2007

3.0 DECISION CONTEXT
The Lennox-Gastaut syndrome (LGS) is rare, and one of the most severe forms of childhood epilepsy[3]. The syndrome is characterised by a debilitating triad of multiple seizure types (of which tonic and atonic [i.e. drop attacks] predominate), a characteristic electroencephalogram (EEG), psychomotor delay and personality disorders[4-6]. It occurs more frequently in males and onset is usually before the age of eight years with a peak between three and five years[5]; onset in the second decade is much less common[5, 7]. Long-term prognosis is often poor; although the epilepsy often improves, complete seizure freedom is rare and conversely the mental and psychiatric disorders associated with LGS tend to worsen with time[5,6]. It is recognised therefore that LGS places a great burden on carers and families, as well as the patient[3-5,8]. Mortality is high at 3% (mean follow-up 8.5years) to 7% (mean follow-up 9.7years), with death frequently related to accidents incurred during seizures (especially drop attacks)[3]. LGS accounts for between one to four per cent of childhood epilepsies and 10% of epilepsies with onset before the age of five years[3]. In Wales, the company estimates approximately 156 patients currently have LGS[9].

Seizures are often resistant to therapy, and patients with LGS are rarely adequately controlled by a single anti-epileptic agent. Sodium valproate is usually chosen as first-line therapy, with lamotrigine, topiramate and benzodiazepines added as adjunctive therapy[10-14]. Treatment however with benzodiazepines has been reported to worsen LGS at times[15]. In addition, even when a drug is initially effective, this may not persist long term[15]. Non-pharmacological treatments include ketogenic diet, and vagal nerve stimulation[4,10,16-17]. A surgical approach, corpus callosotomy, may be warranted in patients who are refractory to all these drug therapies; however this seldom produces total control of seizures[4,10,15].

Rufinamide is licensed as an adjunctive therapy in patients four years and older with LGS[1]. It is a triazole derivative structurally unrelated to other currently available anti-epileptic drugs (AEDs). The principle mechanism of action is thought to be the modulation of the activity of sodium channels, and in particular, prolongation of the inactive state of the channel[15]. The company suggests that initially rufinamide could be used in patients who have not obtained sufficient seizure control with current second line therapy options, particularly lamotrigine, which is a more cost-effective therapy[9].

Rufinamide does not meet the AWMSG criterion for ultra-orphan status, as it is for a condition affecting more than 1 in 50,000 persons in the UK (i.e. 60 persons in Wales) at the time of submission.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main efficacy data included in the company submission is from a Phase III, multicentre, double-blind study and an open-label extension study involving 138 patients with LGS. Results demonstrated that rufinamide used as adjunctive therapy to other AEDs demonstrated a significant median reduction in total seizure and tonic-atonic seizure frequency when compared to placebo; also there was a significant improvement in severity of seizures compared to placebo. The majority of adverse events reported with rufinamide were neurological disorders (headache, somnolence, dizziness and fatigue) and gastrointestinal disorders (vomiting and nausea). Although the European Public Assessment Report (EPAR) highlights some remaining safety issues, the Committee for Medicinal Products for Human Use (CHMP) have considered proposed plans adequate to address these. There are no direct comparative data against any other treatment in the patient population for which rufinamide is licensed. Currently there is no evidence of the development of tolerance to rufinamide; nevertheless a longer-term controlled study would help to provide more robust data over time.

4.2 Review of the evidence on cost-effectiveness

A Markov state-transition model to estimate the cost utility of rufinamide versus topiramate or lamotrigine as adjunctive treatment for children with LGS uncontrolled by up to three antiepileptic drugs is presented. As no head-to-head trials of rufinamide, topiramate or lamotrigine are available, a Bayesian indirect/mixed treatment comparison analysis was performed to assess the relative effectiveness of each. However, it is not clear that the evidence for the analysis is based on a systematic review of the literature, and this is a potential source of bias. Utility values to weight life years gained have been derived by several methods and there appears to be a significant difference in those derived by time trade off (TTO) techniques, and those derived by the EQ-5D instrument. Those used in the base case analysis appear to favour rufinamide due to their application to health states that are defined by arbitrary seizure response thresholds.

In the base case analysis using a three year time horizon and EQ-5D-derived utility values, the incremental cost per QALY gained for rufinamide versus topiramate is estimated as £14,716. The incremental cost per QALY gained for rufinamide versus lamotrigine is £57,696. However, using the more plausible TTO-derived utility values the incremental cost per QALY is reported to be £29,572 for rufinamide against topiramate and to £164,554 against lamotrigine. Sensitivity and scenario analyses indicate that the model is very sensitive to the assumptions around transition probabilities, and all estimates increased with a longer (possibly more appropriate) time horizon of analysis.

5.0 LIMITATIONS OF DECISION CONTEXT

- There are no direct comparative data against any other treatment in the patient population for which rufinamide is licensed.
- A longer-term controlled study would help to provide more robust data on whether patients may develop tolerance to rufinamide over time.

6.0 CLINICAL EVIDENCE

Evidence of the clinical efficacy of rufinamide for the treatment of LGS provided by the company submission included one randomised Phase III, double-blind, placebo controlled trial (Study 022) and an open label extension to this study (Study 022E)[18-20]. Both studies are unpublished. An overview of these studies and the main outcomes are discussed below; further information on these studies can be found in Tables 1A and 1B, Appendix 1.

6.1 Clinical efficacy

6.1.1 Rufinamide versus placebo as adjunctive therapy in patients with LGS (Study 022)[18,19]

This study evaluated the safety and clinical efficacy of rufinamide relative to placebo as adjuvant therapy in 138 patients aged between four and 37 years with inadequately controlled seizures associated with LGS (including atypical absence seizures and tonic-atonic seizures [drop attacks]). Following a baseline phase of 28 consecutive days, participants entered a 12-week double-blind phase and were randomised to receive rufinamide (n=74), or placebo (n=64). Study drug was administered orally as 100, 200, or 400mg tablets in a twice daily dosage regimen. Dosing started at 10 mg/kg daily, and was titrated up to a maximum maintenance dose of 45mg/kg daily over one to two weeks. This was in addition to participants continuing with their standard anti-epileptic drug (AED) regimens (up to three fixed dose AEDs). The mean age of patients was 13 years (range: four to 35 years) for those in the rufinamide group[19], with 41.9% (31 out of 74) of patients aged between four and under 12 years. A total of 123 patients completed the study (63 and 60 in the rufinamide and placebo treated group, respectively)

The results fulfilled primary efficacy outcomes (see Table 1A, Appendix1) as patients in the rufinamide group experienced a 32.7% median reduction in the total seizure frequency per 28 days relative to the baseline phase, compared with an 11.7% median reduction for the placebo group (p=0.0015). Tonic-atonic seizures also dropped by 42.5% in the rufinamide group and increased in the placebo group by 1.4% (p<0.0001), and there was a significant improvement in seizure severity at the end of the double blind phase observed compared with placebo (53.4% versus 30.6% of patients respectively, p=0.0041; giving a numbers needed to treat (NNT) value of five[9]).

In addition, secondary efficacy outcomes which included the percentage of patients who were considered to have responded to treatment (i.e. those who had 50% or greater reduction in seizure frequency per 28 days) found rufinamide to be more effective than placebo in reducing the frequency of all types of seizures and, in particular, drop attacks. The percentage of patients who experienced at least a 50% reduction in the frequency of such tonic-atonic seizures per 28 days, relative to baseline, were 42.5% of patients in the rufinamide group versus 16.7% in the placebo group, (p=0.0020); giving a NNT of four[9].

6.1.2 Long term treatment with rufinamide in LGS (Extension Study 022E[20])

Patients who completed Study 022, and who were considered might benefit from treatment with rufinamide, were eligible to enter this long-term extension study. A total of 124 out of 138 patients who were randomised in the initial trial were enrolled. The extension study consisted of two phases: a double-blind conversion period and an open-label period. Under double-blind conditions, patients who were on placebo (n = 61) were titrated to the appropriate dose of rufinamide over 14 days; while patients on rufinamide stayed on the same dosage of the study drug (n = 63). The median duration of exposure to rufinamide was 432 days. A total of 66.9% (83) of the 124 patients received rufinamide for greater than one year, 59.7% (74) for more than 18 months, and 41.1% (51) of patients were treated for two years or more. Fifteen patients (13%) were treated for three years or more. During the treatment period of up to 36 months, patients treated with rufinamide during the double-blind phase continued to experience clinical improvement in terms of reduced total and tonic-atonic seizure frequency (refer to Table 1A, Appendix 1). There appeared to be no development of tolerance over the study duration. There was a decrease in the total daily dose of the concomitant AEDs for about half of the patients through 30 months of adjunctive therapy.

6.1.3 Points to note from the studies (refer to section 6.1.1 and 6.1.2)

- Most participants in both trials were receiving two concomitant AEDs; valproate, topiramate and lamotrigine were most frequently used [18-20].
- The company state that exploratory analyses (not shown) revealed no treatment-by-region interaction and no association of patient baseline characteristics (including seizure number and number of concomitant AEDs) with the results of the primary efficacy analyses in Study 022 (section 6.1.1)[18].
- Only 42 out of 124 patients (33.9%) completed the 36 month extension study. Of the 82 patients who prematurely discontinued, 51 patients (41.1%) did so due to unsatisfactory therapeutic effect[20]. The EPAR considers it is possible that a proportion of these 51 patients withdrew due to tolerance development with reduced efficacy[15].
- The EPAR highlights that the maximum length of controlled study was no longer than three months and the CHMP concludes that the results from the extension study do not answer the question of whether there is development of tolerance to the anticonvulsant effect of rufinamide during long-term treatment[15].
- The majority of patients in the studies available were aged between four and 18 years (approximately a third [32%] of the trial population were 17yrs or older).
- The extension study protocol did not identify any efficacy variables. Those mentioned in section 6.1.2 were identified by the company after the study was completed.
- Pharmacokinetic and pharmacodynamic analyses have shown the reduction in seizure frequency and seizure severity to be concentration-dependent[15,18]. The bioavailablilty of rufinamide is dose dependent; as the dose increases, the bioavailability decreases[1].

6.2 Safety

The most common adverse events reported overall for rufinamide are headache, dizziness, fatigue, and somnolence[1]. Consequently the SPC warns patients and carers to exercise caution until they are familiar with the potential effects of rufinamide[1].The most common adverse events observed at a higher incidence than placebo in patients with LGS are somnolence (24.3% with rufinamide versus 12.5% with placebo in Study 022) and vomiting (21.6% versus 6.3%, respectively)[18]. Cognitive/psychiatric adverse events of interest however, such as psychomotor hyperactivity and lethargy, were reported less in Study 022 in the rufinamide group compared to placebo (17.6% versus

23.4%, respectively). The safety profile from the extension study (Study 022E) was considered similar to that found from the 12 week, controlled trial (Study 022)[20].

Overall 9.7% (12 out of 124) patients discontinued from the studies due to adverse events; all of whom were receiving rufinamide[20]. The most common adverse events leading to discontinuation were vomiting and rash[1,20]. Serious antiepileptic drug hypersensitivity syndrome has occurred in association with rufinamide, therefore all patients who develop a rash while taking this therapy should be closely monitored. If this syndrome is suspected, rufinamide should be discontinued and an alternative treatment sought[1]. Status epilepticus cases have been observed during clinical development studies, with rufinamide treatment whereas no such cases have been observed with placebo. These events have lead to the discontinuation of treatment in 20% of the cases[15]. In addition, clinical studies suggest that rufinamide may induce notable weight loss; decreased appetite and anorexia occurred in 15% and 13% of patients, respectively. This has been observed in more than 7% of patients (in a limited number) under the age of 12 years old[15]. The CHMP has accepted a risk management plan which recommends further investigations including monitoring of status epilepticus, hypersensitivity reactions, decreased appetite and weight loss[15].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

- Lamotrigine (Lamictal®)
- Topiramate (Topamax®▼)

7.2 Comparative effectiveness

- Topiramate or lamotrigine are the only other drugs licensed as adjunctive treatment in LGS, but no head-to-head comparative trials have been performed on rufinamide versus either of these AEDs. The company however state that the magnitude of the difference in reduction of seizure frequency seen in the placebo controlled trial (Study 022) compared to placebo controlled trials for lamotrigine and topiramate indicate that the clinical benefit of rufinamide may be comparable to these agents [9,21, 22].
- Currently there are no comparative trials recruiting patients that include rufinamide in the treatment of LGS [23].
- Lamotrigine and topiramate are licensed for patients two years and older, whereas rufinamide is licensed for those who are four years and older[1, 13, 14].
- Rufinamide, lamotrigine and, in some cases topiramate, concentrations are all affected by other AEDs. An advantage of rufinamide may be that it offers a more rapid titration schedule (dose titration every two days) compared to lamotrigine or topiramate (dose titration every one to two weeks)[1,13,14].
- Although open-label studies suggest that rufinamide maintains long term efficacy, no controlled study has been conducted for longer than three months duration[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by rufinamide (Inovelon®▼) over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of rufinamide (Inovelon®▼) is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of rufinamide.

8.3 Review of company submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission describes an economic model with rufinamide versus topiramate or lamotrigine as adjunctive treatment for children with LGS.

Patients enter the model and receive either rufinamide or topiramate or lamotrigine as adjunctive treatment for three months. During this time it is assumed that patients can only switch treatment due to adverse events. After three months of treatment patients can remain on initial treatment and experience different responses (75% reduction, at least 50% to 75% reduction, or less than 50% reduction in tonic-atonic seizures compared to baseline), or switch to standard treatment due to adverse events, or experience death. Switching due to standard treatment is not possible after the first three month period. The standard treatment is a mix of AEDs as observed in the placebo group of study 022; for patients treated with rufinamide, it is a mix of AEDs as used in the whole placebo arm in study 022; for patients treated with topiramate, it is a mix of AEDs as used in the placebo arm without topiramate; and for patients treated with lamotrigine, it is a mix of AEDs as used in the placebo arm without lamotrigine. Every three months patients can switch between the three response health states or death. Once a patient does not show a sufficient response on a treatment (less than 50% reduction in tonic-atonic seizures compared to baseline) they can either stay on the treatment or switch to standard treatment, and may again experience one of the three response health states or death[24].

All treatment transitions after the initial three month period across health states, for rufinamide, topiramate and lamotrigine treated patients, were based on data from the rufinamide extension trial 022E, i.e. efficacy for each of the treatments is assumed to be the same after the initial three month period[24]. The model assumes that transition probabilities in all subsequent three-month cycles are constant, which may be subject to some uncertainty. Utility values for weighting life years have been elicited via a study and there is a significant difference in those derived by time trade off (TTO) techniques, and those derived by the EQ-5D instrument. The EQ-5D-derived utility values are assumed for the base-case analysis and appear to bias the model in favour of rufinamide. The TTO-derived utility values appear plausible and significantly alter the model outputs. Sensitivity analyses demonstrate the sensitivity of the model results to key assumptions, especially in relation to the transition probabilities. The model has been provided to WMP.

8.3.2 Population

The population modelled has a mean age of 14.5 years, a mean weight of 42kg, and the median number of tonic-atonic seizures is 92 per patient per 28 day period, as observed at baseline in Study 022[18,24].

8.3.3 Perspective and time horizon

The model considers the cost effectiveness of rufinamide from the perspective of NHS and personal and social services. A time horizon of three years has been used in the base case analysis; on the basis that the maximum follow up in the rufinamide trial is 36 months and in the topiramate extension trials is 40 months with a shorter median, and the seizure types for LGS patients change over time. One and five year time horizons have also been explored in scenario analyses[9]. Patients with LGS require life-long treatment.

8.3.4 Comparators

Topiramate and lamotrigine are the comparators in the model, and both are licensed as adjunctive therapy in LGS[13,14]. The Scottish Intercollegiate Guidelines Network guideline on epilepsies in children and young people suggests that these are effective add-on treatments[25].

During the double-blind phase of the rufinamide trial, valproate, lamotrigine, and topiramate were the most frequently used concomitant AEDs for both rufinamide- and placebo-treated patients[18]. This suggests that rufinamide may be used in addition to topiramate and lamotrigine, rather than instead of these agents.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

8.3.5.1.1 Efficacy at three months

As no head-to-head trials of rufinamide, topiramate or lamotrigine were available, a Bayesian indirect/mixed treatment comparison (MTC) has been conducted to determine the relative odds of achieving a 75% reduction, or at least 50% to 75% reduction in tonic-atonic seizures compared to baseline for each of the drugs. A literature review is reported to have identified one key randomised, placebo-controlled trial for each of these agents, which have been used in the MTC[18,21, 22]. However, as few details of the review are presented, it is not possible to confirm whether it is systematic, and the possibility that selective reporting might lead to biased estimates of effectiveness cannot be excluded.

The odds ratios relative to placebo were translated into probabilities of achieving a 75% reduction, or at least 50% to 75% reduction in tonic-atonic seizures compared to baseline for each of the drugs by using the placebo response of the rufinamide trial as a reference point and combining this with the odds ratios from the MTC.

There were some differences in the characteristics of patients in the three clinical trials used in the MTC (see Table 2A in Appendix 2). In the trial of topiramate only a very small minority were taking three concomitant AEDs (around 3%) compared with around a third of patients in the rufinamide trial[18,21]. These data are not available for the lamotrigine trial[21]; but the median number of tonic-atonic seizures at baseline experienced by patients in the lamotrigine trial (58 in the lamotrigine group and 46.4 in the placebo group per 28 days) appears considerably lower than in the topiramate and rufinamide trials (median of at least 90 per 28 days)[18,21]. The lamotrigine trial does not provide data on the proportion of patients achieving at least 75% decrease from baseline in the number of tonic-atonic seizures, and it is unclear what proportion is assumed to achieve this for lamotrigine in the model. The extent to which these differences may influence the results of the mixed treatment comparison is unclear.

It should also be noted that the cut-off levels for the response-defined health states are arbitrary thresholds and a patient who experiences a 74.9% or a 49.9% reduction from baseline in tonic-atonic seizure frequency would be considered very differently in this model to a patient who experiences a 75.0% or 50.0% decrease.

8.3.5.1.2 Efficacy beyond three months

Transition probabilities beyond three months are derived from the rufinamide extension study[9]. The rufinamide data are applied to all comparator treatment arms due to a lack of relevant extension data for topiramate and lamotrigine. The transition probabilities are calculated for response categories determined between the first and second three month period of six months of treatment in all patients. These transition probabilities are then assumed to be constant in each subsequent three month cycle. The same transition probabilities are also used after discontinuation of rufinamide, topiramate or

lamotrigine[24]. The assumptions employed for the initial three months of treatment therefore determine the course of events in subsequent periods.

The company submission considers this to be a conservative approach as efficacy is assumed to be the same for each of the treatments after the initial three month period[9]. The scientific discussion of the EPAR noted that only 42 of 124 patients completed the rufinamide extension study, whereas 82 withdrew and of these, 51 patients withdrew due to insufficient therapeutic effect[15]. It further considered it was possible that a proportion of these 51 patients withdrew due to tolerance development with reduced efficacy and concluded that the results from the extension study do not answer the question of whether there is development of tolerance to the anticonvulsant effect of rufinamide during long-term treatment[15]. The company has provided data which reportedly indicate that, for tonic-atonic seizure, the 50% and 75% responder rates for the whole treatment period (44.4% and 29.1%, respectively) were similar to the response rates of 42.5% and 21.9% found with rufinamide during the preceding short-term double-blind trial. The company considers that these findings indicate that seizure control is maintained during long-term therapy with rufinamide. Whatever the underlying reasons for insufficient therapeutic effect, a significant proportion of patients withdrew from the extension study and controlled long-term data are lacking.

8.3.5.2 Adverse events

In the model, treatment discontinuation due to adverse events can only occur in the first three months and the model only considers adverse events in the initial three months of treatment. As there is a lack of head-to-head data on adverse events, a Bayesian MTC has been conducted to estimate odds ratios relative to placebo for discontinuations and for adverse events of weight loss/gain, somnolence, concentration problems, rash and nausea/vomiting, based on the same three trials identified in a literature review[18,21, 22]. Issues relating to the absence of detail of the literature review apply equally here as they did for the estimation of relative effectiveness.

In order to obtain expected probabilities by treatment, the relative effects were combined with the outcomes of the placebo arm of the rufinamide trial[26]. In the original submission, there was some confusion in the reported incidence of clinically significant weight gain/loss. As the only utility values associated with adverse events in the model are those that relate to weight changes, this was a source of uncertainty. The company has provided revised utility estimates related to with clinically significant weight loss and revised model outputs. The clinical study report for the rufinamide extension study notes that, with the exception of somnolence, the incidence of the common adverse events (e.g. upper respiratory infections, pyrexia, but not somnolence) was greater during long term treatment with rufinamide than was observed in the 12-week double-blind phase of Study 022, and suggests this is probably due to the longer period of follow up and exposure[18]. There were few cases of discontinuations due to adverse events with rufinamide in the long term follow up. However, the extension study provides non-comparative data and the extent to which the model assumptions on adverse events accurately reflect adverse events with all relevant AEDs in the long term is uncertain.

8.3.5.3 Utility weights

A study elicited utility values for LGS health states from 119 members of the general public and caregivers/parents (48%) in six geographical areas of the UK (none in Wales)[24]. Four health state descriptions in LGS were developed (see Table 2B in Appendix 2). A time trade off (TTO) technique was used to elicit utility values for the health states, supplemented by visual analogue scale (VAS) and EQ-5D methods. Five major adverse events associated with AEDs were also defined and were evaluated using the TTO method (see Table 2C in Appendix 2).

The use of members of the public and caregivers/parents to provide utility values is appropriate, as patients with LGS are unlikely to be able to complete the various elicitation exercises and it reflects society's preferences. The health state descriptors were developed following a review of the medical literature, and were reported to be validated by four UK clinicians and via pilot interviews[24]. The arbitrary thresholds for response that define the health states however are a limitation of this type of exercise, as demonstrated below.

Table 2B in Appendix 2 demonstrates that the VAS-derived and the TTO-derived utility values are very consistent with each other over the different health states. In contrast, the variation in the utility values between the health states is very marked with the EQ-5D method of elicitation and these are somewhat at odds with those elicited by the other methods for health states that reflect a less than 50% decrease from baseline in tonic-atonic seizures. For example, using the EQ-5D method, the difference in mean utility values between a patient who achieves a 50.0% reduction in tonic-atonic seizures and a patient who achieves a 49.9% reduction in tonic-atonic seizures is 0.400, compared with a difference of 0.144 using the TTO method and 0.142 using the VAS.

The company submission states that the EQ-5D-derived utility values are used for the base-case analysis[9]. The use of the EQ-5D-derived utility values would be more favourable to the drug that is assumed to have the greatest probability of achieving and maintaining a patient response greater than 50%. The base-case analysis using the EQ-5D-derived utility values would therefore appear biased in favour of rufinamide (the model estimates the time in health states with greater than 50% decrease in tonic-atonic seizures from baseline as being 6.24 months for rufinamide compared with 3.48 months with topiramate and 4.56 months with lamotrigine[24]). As would be expected, the approach used to derive utility values for the model has a significant impact on the model outputs (refer to section 8.3.8).

8.3.6 Healthcare resource utilisation and cost

Healthcare resource was estimated on the basis of a survey administered to five UK clinicians who treat paediatric patients with epilepsy (non-Welsh). Published unit cost data are used in the main to estimate the costs of resources and as resource use is based on opinion rather than actual collected data, uncertainty in resource use was calculated as $\pm$0.4 times the point estimate[24].

8.3.6.1 Drug costs

The average dose of rufinamide, topiramate and lamotrigine, as well as other drugs that make up the background "standard AEDs" to which these agents are added, are based on the clinician survey data. The background AEDs and the standard treatment that patients are switched to having failed on the comparator agents is based on a weighted mix of concomitant AEDs as used in the rufinamide Study 022. The standard treatment to which topiramate and lamotrigine patients are switched to upon failure is composed of the placebo arm treatments from Study 022, with topiramate or lamotrigine excluded as appropriate. In the first three months, the original drug costs and background standard treatment costs were applied to all patients. In each of the following three-month cycles, the drug acquisition cost was calculated as weighted drug costs based on the percentage of patients staying on the original drug (plus background standard treatment) and those switching to standard treatment[24].

The mean patient weight is assumed to be 42.3kg as in Study 022, and for each drug, the cost was based on the cost of purchase dose, i.e. the combination of tablets with different strengths and their corresponding list prices[18]. Nevertheless, the simplest

combination of tablets providing the total daily dose has been used, which does not take account of the fact that doses may not be given once daily (e.g. the daily dose of rufinamide based on the above assumptions is 1700mg and is costed on the basis of four 400mg tablets and one 100mg tablet; however, rufinamide is given twice daily[1,27]). This may lead to some minor inaccuracies in drug cost estimates used in the model.

8.3.6.2 Adverse event costs

Of the five adverse events considered in the model, only three were assumed to be associated with resource use and costs: weight loss/gain, somnolence and rash. These adverse events were assumed only to occur in the first three months and costs are only accrued during this time. These are estimated based on resource use estimates from the clinician survey and published unit costs[24].

8.3.6.3 Other resource use and costs

Other medical resource use was linked to initial three month treatment/care, which is independent of health state, and health state-related care. This includes health care professional contacts, inpatient care, diagnostic procedures and tests, and personal and social service input such as respite and home care. These are based on the clinician survey and costed with published unit cost data[26].

8.3.7 Discounting

Costs and outcomes are discounted at 3.5% per annum, which is the preferred discount rate[24].

8.3.8 Results

The company submission has presented the base case analysis, however the company has requested that Section 8.3.8 remains as confidential data (CIC).

8.3.8.1 Base case analysis – using EQ-5D-derived utility values

(CIC)

8.3.8.2 Scenario of base case analysis – using TTO-derived utility values

(CIC)

8.3.8.3 Scenarios of different discount rates and time horizons

(CIC)

8.3.9 Sensitivity analysis

(CIC)

8.3.9.1 One way sensitivity analyses

(CIC)

Table I. Results of key one-way sensitivity analyses in the model – probability of achieving and maintaining at least a 75% reduction in tonic-atonic seizures[24]
(CIC)

8.3.9.2 Probabilistic sensitivity analysis (PSA)
Distributions were fitted to the transition probabilities, utilities and costs for sampling purposes. Beta distributions are reported to have been fitted to the transition probabilities and utilities. The mean EQ-5D-derived utilities approach zero for health state of less than 50% decrease in tonic-atonic seizures from baseline, and some estimates in the utility study undertaken in members of the public/carers/parents are reported to have been less than zero[24]. Cost effectiveness acceptability curves were generated by running 1000 simulations. The key results are presented in Table II, and reflect the uncertainty in the model parameters. Over 90% of the uncertainty around costs, QALYs and net monetary benefit can be explained by the uncertainty in transition probabilities.

Table II. Results of PSA for the EQ-5D and TTO-derived utility models [24]

	EQ-5D-derived utilities		TTO-derived utilities	
	Willingness to pay £20,000/ QALY	**Willingness to pay £30,000/QALY**	**Willingness to pay £20,000/QALY**	**Willingness to pay £30,000/QALY**
Probability rufinamide is the most cost effective treatment at 3 years	21.5%	33%	6%	12.5%
Probability rufinamide is more cost effective than topiramate	68%	75%	52%	65%
Probability rufinamide is more cost effective than lamotrigine	25%	38%	8%	15%

8.4 Review of evidence on budget impact
8.4.1 Description and critique of the company's submission
In the absence of Wales-specific data, the budget impact analysis uses an estimated European prevalence rate, and an incidence rate derived from a Finnish epidemiological study to estimate the prevalence and incidence of LGS and applies these rates to the estimated patient population in Wales. The analysis takes the cumulative discounted total NHS and personal and social costs of treatment used in the economic model and averages the annual costs of treatment from this.

8.4.2 Perspective and time horizon
The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years from 2009 to 2013[9].

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

Based on Welsh Assembly Government population projections the company submission estimates that there are approximately 540,000 children aged four to 18 years in Wales in 2008[29]. A prevalence rate for LGS of 0.26 per 1000 live births was originally estimated as the mean of those found in two epidemiological studies (one based in USA and one based in Finland) [30, 31]. This would have equated to 146 children with LGS in Wales in 2008[9].

The EPAR reports that, within European populations, the prevalence of LGS is 0.9 per 10,000 population across all age groups[15]. Based on a population of 2.993 million in 2008 this would equate to 269 patients across all age groups in Wales. The company has submitted revised estimates based on this prevalence.

A retrospective, community based study conducted in Finland found that the incidence of LGS was two per 100,000 in children aged 0-14 years[32]. This rate has been applied to the Welsh Assembly Government population projections and would equate to 11 new cases of LGS in 2009[29].

It is assumed that no patients will die during the five years and that all patients will remain on AED treatment during that time. The original approach to estimation of patient numbers did not account for those patients who reach the age of 19 years+ during the five year time horizon, which would have resulted in a (theoretical) underestimate of patients eligible for treatment. Based on the revised prevalence estimates, patients of all ages are considered.

This is assumed to that it is the patients who require combination treatment that are eligible for treatment with rufinamide.

8.4.3.2 Rates of adoption

(CIC)

8.4.3.3 Costs and resource use

The budget impact analysis considers the costs of treatment with rufinamide to be the drug costs plus the costs of health professional contacts, inpatient stays, diagnostic tests, adverse events, and personal and social costs, as per the economic model[9]. The economic model considers the cumulative costs over a three-year time horizon, which is discounted at a rate of 3.5% per annum. These discounted cumulative costs from the economic model have simply been divided by three to produce average annual costs, which would introduce some inaccuracy. To estimate the overall budget impact of the introduction of rufinamide, the average annual costs topiramate and lamotrigine have been summed and divided by two to produce an estimate of the budget impact of treatment without rufinamide. The number of patients estimated to receive rufinamide each year has then been used to determine the additional budgetary impact.

8.4.4 Results

(CIC)

8.4.5 Sensitivity analysis

No sensitivity analysis was conducted.

8.4.6 Comparator costs

Example comparator costs for a patient weighing 40kg based on BNF quoted doses and prices are presented in Table III[27].

Table III. Example comparator maintenance dose costs for patient weighing 40kg

Product	Adjunctive therapy daily dose example	28-day example cost*
Rufinamide	Child aged four years+, body-weight 30–50 kg max. 900 mg twice daily	£208.21 (based on 900mg bd)
Topiramate	Child aged two to 16 years: 9mg/kg in two divided doses after titration	£99.41 (based on 175mg bd)
Lamotrigine (generic tablets)	Child aged two to 12 years taking valproate: usual maintenance 1–5 mg/kg daily in one to two divided doses (max. single dose 100mg)	£5.60 (based on 100mg bd)
Lamotrigine (generic tablets)	Child aged two to 12 years taking enzyme inducing drugs (without valproate): usual maintenance 5–15 mg/kg daily in two divided doses (max. single dose 200mg)	£12.68 (based on 200mg bd)
Doses and costs are for general comparison and do not imply therapeutic equivalence *All costs obtained/calculated from British National Formulary No. 55, 2008 and relate to doses possible by use of whole tablets bd=twice daily		

9.0 ADDITIONAL INFORMATION

9.1 Guidance and audit requirements

- In October 2004 the National Institute for Health and Clinical Excellence (NICE) published guidelines on epilepsy in adults and children. The guidelines include recommendations that children and adults with epilepsy should be assessed by a specialist paediatrician with training and expertise in epilepsy for correct diagnosis, and that AED therapy in children should be initiated by a specialist [33].
- As part of the post-licensing commitment, a registry study is to be set up by the company in 2008. It will continue to run for three years, with the aim of collecting data from 100 rufinamide treated patients across Europe[9].
- Rufinamide (Inovelon®▼) may be appropriate for use within NHS Wales prescribed under specialist recommendation.

9.2 Related advice

Note: The following documents do not include rufinamide, which was not licensed at the time of their publication.

- NICE has published two technology appraisals; in March and April 2004 regarding newer drugs for epilepsy in adults and in children, respectively[34,35]. Both appraisals included topiramate and lamotrigine.
- The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy has been reviewed in a Health Technology Assessment published in 2006[3].

- The Scottish Intercollegiate Guidelines Network (SIGN), in 2005, produced a clinical guideline on the diagnosis and management of epilepsies in children and young people[25].

9.3 Previous AWMSG/NICE advice
None

9.4. Ongoing studies
As part of the post-licensing commitment, a registry study is to be set up by the company in 2008. It will continue to run for three years, with the aim of collecting data from 100 rufinamide treated patients across Europe[9].

9.5 Patient Organisation Information
A submission by a patient representative (a former member of the patient interest groups: the National Society of Epilepsy and the Joint Epilepsy Council of the UK and Ireland) was provided to AWMSG members.

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Appendix 1. Additional Clinical Information

Table 1A. Clinical studies for Rufinamide for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS)

Reference	Study type	No. of patients	Patient characteristics	Treatment regimen	Concomitant AEDs			Outcomes			
						Rufinamide	Placebo		Rufinamide	Placebo	p value
18	Phase III, randomised, double-blind study	Randomised n=139 ITT population n=138 Rufinamide n=74 Placebo n=64	**Male patients:** Rufinamide: n=46 (62.2%) Placebo: n=40 (62.5%) **Median age:** Rufinamide:14.5yrs (range 4-35) Placebo: 13.6yrs (range 4 -37). Rufinamide: ≥4 to <12yrs: 41.9% ≥12 to <17yrs: 5.7% ≥17yrs: 32.4% **Baseline seizures:** Tonic-atonic Atypical absence Myoclonic Tonic Tonic-clonic Atonic	Rufinamide 10mg/kg was titrated to approx. 45mg/kg daily (max). Target dosage of 45mg/kg daily was achieved in 87.8% of the rufinamide-treated patients. **Median dose:** 1800mg per day.	**AEDs** Valproate Lamotrigine Topiramate Clonazepam Carbamazepine Phenytoin Clobazam Phenobarbital **Concomitant AEDs used, n (%)** One Two Three	44 (59.5%) 30(40.5%) 20 (27%) 14 (18.9%) 12 (16.2%) 10 (13.5%) 10 (13.5%) 6 (8.1%) 8 (10.8%) 38 (51.4%) 28 (37.8%)	35(54.7%) 19(29.7%) 17(26.6%) 7 (10.9%) 12 (18.8%) 12 (18.8%) 8 (12.5%) 9 (14.1%) 8 (12.5%) 35 (54.7%) 21(32.8%)	**Primary endpoint:** Change in total seizure frequency per 28 days (%) Change in tonic-atonic seizure frequency per 28 days (%) Proportion of patients with improvements in seizure severity (%) **Key secondary endpoint:** Change in atypical and typical absence frequency per 28 days (%) Change in atonic seizure frequency per 28 days (%) Proportion of patients with total seizure reduction ≥50% (%) Proportion of patients with total seizure reduction ≥75% (%) **Responder Rates:** Total seizure reduction of ≥50% (%) Tonic-atonic seizure reduction ≥50% (%)	33 43 53 51 45 31 18 31.1 42.5	-12 1.4 31 30 21 11 3 10.9 16.7	0.0015 <0.0001 0.0041 0.0222 0.0125 0.0045 0.0135 - 0.002

Table 1A. Continued

Reference	Study type	No. of patients	Patient characteristics	Treatment regimen	Concomitant AEDs			Outcomes			
						Rufinamide	Placebo		Rufinamide	Placebo	p value
19	Open-label extension study	Included n=124 (one patient directly entered in to Study 022E)	**Median age**: 14.2yrs (range 4-37)	**Median time of treatment** with rufinamide = 432 days. Duration of treatment ranged from 10 to 1149 days.		(n=124)	(n=0)		(n=124)	(n=0)	
					AEDs:			**Primary endpoint:**			
					Valproate	75 (60.5%)	-	Change in total seizure frequency per 28 days (%)			
					Lamotrigine	46 (37.1%)	-				
					Clonazepam	45 (36.3%)	-				
					Topiramate	45 (36.3%)	-				
					Carbamazepine	20 (16.1%)	-	12 months	-55	-	-
					Phenytoin	18 (14.5%)	-				
					Phenobarbital	14 (11.3%)	-	24 months	-69	-	-
					Levetiracetam	13 (10.5%)	-				
								36 months	-79	-	-
								Change in tonic-atonic seizure frequency per 28 days (%)			
								12 months	-58	-	-
								24 months	-75	-	-
								36 months	-76	-	-

Appendix 2. Additional Health Economic Information

Table 2A. Selected patient characteristics and outcomes in trials used in the Bayesian MTC

Reference	Study 022 CSR		Sachdeo et al 1999		Motte et al 1997	
	Rufinamide	Placebo	Topiramate	Placebo	Lamotrigine	Placebo
Patient characteristics						
Mean age (yrs)	14.5	13.6	11.2	11.2	9.6	10.9
Median no. tonic-atonic seizures per 28 days	92	92.5	90	98	58	46.4
Double-blind phase duration (wks)	12 weeks		11 weeks		16 weeks	
Concomitant AEDs (%):						
1	10.8%	12.5%	40.0%	39.6%	?	?
2	51.4%	54.8%	58.0%	56.3%	?	?
3	37.8%	32.8%	2.0%	4.2%	?	?
Outcomes						
≥50% reduction in tonic-atonic seizures	42.5%	16.7%	28%	14%	33%	16%
≥75% reduction in tonic-atonic seizures	21.9%	3.3%	17%	6%	?	?
?=data not available						

Table 2B. Mean (median) utility values elicited for the health states used in the model [24]

Health State description	VAS	TTO	EQ-5D
1 – anchor state: patients experience 21-28 tonic-atonic seizures per week	0.34 (0.325)	0.393 (0.426)	0.02 (0.079)
2: patients achieving less than 50% reduction in tonic-atonic seizures or experiencing 14 to 28 tonic-atonic seizures per week	0.414 (0.4)	0.461 (0.52)	0.100 (0.137)
3: patients achieving at least 50% to 75% reduction in tonic-atonic seizures or experiencing 7 to 14 tonic-atonic seizures per week	0.556 (0.55)	0.605 (0.65)	0.500 (0.516)
4: patients achieving more than 75% reduction in tonic-atonic seizures or experiencing 1 to 7 tonic-atonic seizures per week, occasionally none	0.677 (0.695)	0.699 (0.75)	0.596 (0.587)

Table 2C. Mean disutility elicited by TTO for the five adverse events used in the model [24]

Adverse event	Concentration problems	Weight loss	Somnolence	Rash	Nausea/vomiting
Mean disutility score	0.108	0.135	0.174	0.190	0.193