AWMSG Secretariat Assessment Report – Limited submission

Rufinamide (Inovelon®) 40 mg/ml oral suspension

Company: Eisai Ltd

Licensed indication under consideration: adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 1 year to < 4 years.

Date of licence extension: 3 August 2018

Comparator(s)

The comparators included in the company's submission are:

- Lamotrigine dispersible tablets
- Topiramate sprinkle capsules (Topamax®).

Limited submission details

The limited submission criteria were met based on a minor licence extension and an anticipated usage in NHS Wales considered to have minimal budgetary impact.

Clinical effectiveness

- In 2012 rufinamide (Inovelon®) oral suspension was recommended by the All Wales Medicines Strategy Group (AWMSG) as an option for restricted use within NHS Wales as an adjunctive therapy to treat seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged 4 years and older. Rufinamide is restricted for use in patients for whom other adjunctive treatments have proved sub-optimal or have not been tolerated.
- This submission covers the licence extension of rufinamide to include children aged ≥ 1 to < 4 years, and is restricted to treatment where other adjunctive treatments are sub-optimal or not tolerated, in line with AWMSG's recommendation for patients aged 4 years and older.
- Treatment for seizures associated with LGS is guided by several factors including patient co-morbidities, concurrent medication, medicine tolerability and formulations available. The National Institute for Health and Care Excellence (NICE) clinical guideline 137 recommends lamotrigine as first-line adjunctive treatment for children, young people and adults with LGS. Rufinamide and topiramate will generally be considered after lamotrigine. Clinical expert opinion in Wales suggests a range of other adjunctive treatments may also be considered; such as off-label levetiracetam and clobazam, a ketogenic diet and vagal nerve stimulation.
- The company's submission includes results from study 303, a two-year phase III, multicentre, open-label study to assess the pharmacokinetics, safety and efficacy of adjunctive treatment with rufinamide oral suspension in children aged ≥ 1 to < 4 years with inadequately controlled LGS. Children were randomised (2:1) to

receive either rufinamide (n = 25) or any approved antiepileptic of the investigator's choice (n = 12). The Committee for Medicinal Products for Human Use (CHMP) found the efficacy results were inconclusive and did not support a clinically relevant effect of rufinamide. This was because the study was small in size and not adequately powered for the efficacy analyses performed.

- Because LGS disease expression in younger children is similar to that in older children, CHMP concluded that it was acceptable to extrapolate data from patients with LGS aged ≥ 4 years, providing the dose could be established. Pharmacokinetic modelling and analysis was performed on pooled data from three phase III studies of rufinamide in the treatment of LGS (including study 303) and one single-dose study in healthy people. CHMP considered this model was adequate to predict exposure for all body weights and supported the proposed dose of rufinamide to treat LGS in children aged ≥ 1 to < 4 years.
- Study 303 provided up to two years of safety data and showed that rufinamide was well tolerated in children aged ≥ 1 to < 4 years. Most adverse events were mild to moderate and there were no new or unexpected safety concerns. CHMP concluded that the safety profile of rufinamide in children aged ≥ 1 to < 4 years was consistent with the known safety profile of rufinamide established in patients aged 4 years and older.

Budget impact

- In the absence of Wales-specific data, the budget impact analysis conducted by the company uses estimated prevalence and incidence rates of LGS taken from a European source: Orphanet, to estimate the patient population in Wales.
- The company estimates 16 children aged 1 year to < 4 years with LGS in Wales would be eligible for treatment with rufinamide in Year 1; and that this number would remain the same from Year 1 to Year 5. Clinical expert opinion sought by the All Wales Therapeutics and Toxicology Centre (AWTTC) suggests that 16 patients per year is an over-estimate.
- The cost of treatment differs according to a child's weight. The annual cost per child for rufinamide, and each of the comparators, was based on average weight (15 kg) for children aged 2 years to < 4 years rather than the average weight for each age between 1 year and < 4 years.
- Based on the company's market share projections, rufinamide is assumed to partly displace topiramate. The company estimates that, assuming a [commercial in confidence figure removed] market share, [commercial in confidence figure removed] children aged 1 year to < 4 years will receive treatment with rufinamide in Year 1, increasing to [commercial in confidence figure removed] children in Year 5, assuming an uptake of [commercial in confidence figure removed]. The net medicine acquisition cost of introducing rufinamide is estimated to be [commercial in confidence figure removed] in Year 1 increasing to [commercial in confidence figure removed] in Year 5.
- Whilst there are some limitations in the company's estimate, the overall budgetary impact is anticipated to be minimal.

Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- The applicant company suggests that rufinamide meets AWMSG's criteria for an orphan medicine because the prevalence of LGS, estimated from a European reference source, is 1.5 per 10,000 people; resulting in 469 people of all ages with LGS in Wales.
- AWTTC considers rufinamide (Inovelon®) eligible to be appraised as an orphan medicine because the full population of the licensed indication eligible for treatment is ≤ 5 in 10,000 people.
- The New Medicines Group and AWMSG will consider additional criteria (see Table 1) if they consider rufinamide meets the criteria to be appraised under the policy for orphan, ultra-orphan and medicines developed specifically for rare diseases.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers	LGS is one of the most severe forms of childhood epilepsy, which continues to manifest into adulthood in many patients. It is associated with significant morbidity and mortality. Hallmarks of the disease include multiple drug-resistant seizure types, and mental retardation or a learning disability. LGS has a significant long-term impact on a patient's social functioning, intellectual development and independent living. This places an enormous toll on the quality of life for patients and their carers.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Lamotrigine and topiramate are already licensed for use in children aged 2 years and older for the treatment of seizures associated with LGS. Rufinamide is licensed for use in children from 1 year of age.
Whether the medicine can reverse or cure, rather than stabilise the condition	Rufinamide does not reverse or cure LGS.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	Rufinamide does not bridge a gap to a "definitive" therapy.
The innovative nature of the medicine	Rufinamide is not considered innovative.
Added value to the patient (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The company states that rufinamide offers a faster dose titration schedule compared with topiramate or lamotrigine. The company indicates this as an advantage because achieving satisfactory seizure control in LGS is challenging.
Added value to the patient's family (e.g. impact on a carer or family life)	Based on results from a study of rufinamide as adjunctive therapy in children aged 4 years and older the company proposes that rufinamide may help to reduce the burden of care for parents and carers.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; LGS: Lennox-Gastaut syndrome; NMG: New Medicines Group	

Additional information

AWTTC is of the opinion that, if recommended, rufinamide (Inovelon®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

Evidence search

Date of evidence search: 19 February 2019
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Rufinamide (Inovelon®) 40 mg/ml oral solution. Reference number 991. May 2019.

Appendix: Previous AWMSG secretariat assessment report (published July 2012)

In July 2012, AWMSG appraised rufinamide (Inovelon®) as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age and older (AWTTC reference number 1663). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of rufinamide (Inovelon®) as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 1 year of age to less than 4 years of age (AWTTC reference number 991).

The original report for AWTTC reference number 1663 is included below for completeness.

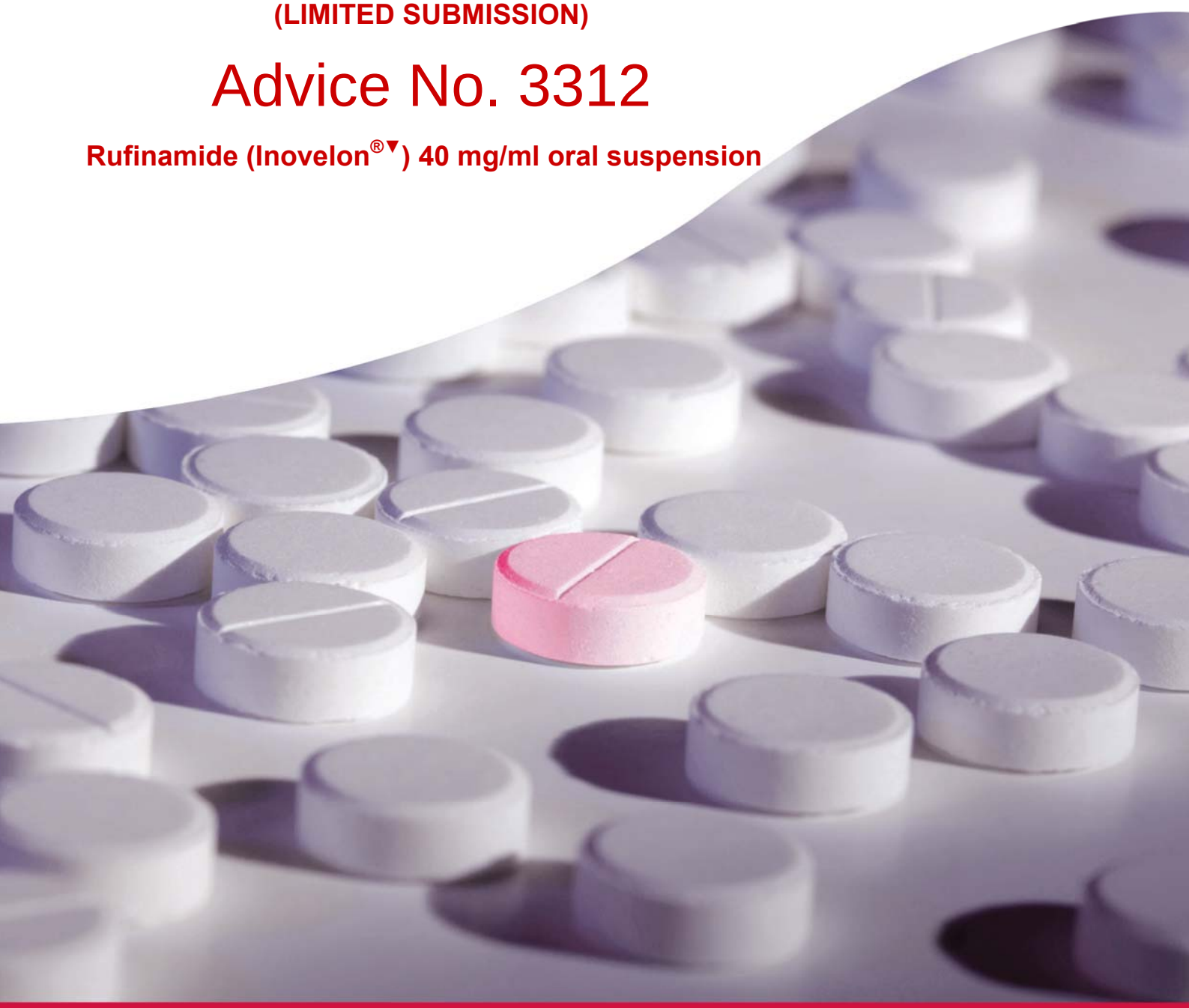
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 3312

Rufinamide (Inovelon®▼) 40 mg/ml oral suspension



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3312
Rufinamide (Inovelon®▼) 40 mg/ml oral suspension

This assessment report is based on evidence from a limited submission by Eisai Ltd on 19 April 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Rufinamide (Inovelon®▼) 40 mg/ml oral suspension is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age and older[2].
Marketing authorisation date	21 November 2011[3] (tablet formulation licensed 16 January 2007).
Comparators	Rufinamide (Inovelon®▼) 100 mg, 200 mg and 400 mg tablets.
Limited submission details	Rufinamide (Inovelon®▼) for the above indication met the following criteria for eligibility for a limited submission: • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of bioequivalence evidence

The company submission[1] includes a randomised, open-label, crossover, single-dose study, which compared the pharmacokinetic characteristics of rufinamide 400 mg tablets with that of a 10 ml dose of rufinamide 40 mg/ml oral suspension in 24 healthy subjects (18–55 years) under fed conditions[4]. Data from endpoints including area under the curve from baseline to 72 hours (AUC_{0-72h}) and peak concentration (C_{max}) were within criteria for assuming bioequivalence between the two formulations[4,5].

Overall, treatment-emergent adverse events (TEAEs) were reported by 13/24 (54.2%) subjects and were all mild or moderate in severity. The most frequently reported TEAE was headache (9/24 [37.5%])[4]. At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) considered the safety profile of the oral suspension comparable to that of the marketed tablets[5].

2.2 Points to note

- At the time of licensing, CHMP considered rufinamide oral suspension to allow more convenient administration to young children and patients with swallowing difficulties, and increases the treatment options for patients who prefer to not swallow solid oral presentations[5]. It was also suggested that patient compliance would be expected to improve, especially in young children[5].

- The submission includes evidence of bioequivalence between rufinamide 400 mg tablets and rufinamide 40 mg/ml oral suspension; no new evidence of efficacy has been submitted, as this was not required at time of licensing. Additionally, safety data included as part of the submission has inherent limitations[1], as the data are derived from an open-label study in a low number of healthy adults[4]. This is of particular relevance given that Lennox-Gastaut syndrome usually presents in children between the ages of one and eight years (typically between three and five years) and then continues to manifest into adulthood[5].
- If a patient has difficulty with swallowing, the Summary of Product Characteristics states that rufinamide film-coated tablets can be crushed and administered in half a glass of water. Rufinamide film-coated tablets and oral suspension may be interchanged at equal doses; patients should be monitored during the switch over period[2].
- Rufinamide (Inovelon®▼) film-coated tablets were licensed on 16 January 2007[2] and approved by the All Wales Medicines Strategy Group (AWMSG) in October 2008 for use 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[6].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company originally estimated there to be 156 patients in Wales with a diagnosis of Lennox-Gastaut syndrome, and based on the simple assumption that 20% of patients would have swallowing difficulties, estimated that approximately 31 patients are potentially eligible for treatment with the 40 mg/ml oral suspension formulation of rufinamide[1]. In response to a request from the All Wales Therapeutic and Toxicology Centre for further information, the company has revised its estimates. Based on data from 2006, the company estimates 18% of the Welsh population to be aged 4–18 years. An average prevalence rate of 0.27 per 1,000 live births is used, derived from US and Finnish studies, to provide an estimated 146 patients with Lennox-Gastaut syndrome in Wales in 2012. Reportedly based on US incidence data from over 25 years ago, the company estimates 11 new Lennox-Gastaut syndrome patients per year. Company market research data are reported to indicate 18% of Lennox-Gastaut syndrome patients receive rufinamide each year, equivalent to 27–29 patients, assuming an average daily dose of 1,800 mg. Of these, the company assumes 20% (5 or 6 patients) would be eligible to receive the 40 mg/ml oral suspension formulation each year. On a per mg basis, the oral suspension is priced at parity with the 100 mg and 200 mg tablet formulations, but is more costly than the 400 mg tablets. Based on the annual cost of treatment per year outlined in Table 1 below, the company estimates an annual net budget impact of around £2,720 in 2012, rising to £2,933 in 2016 for the treatment of 5–6 patients.

3.2 AWTTC critique of the budget impact analysis

In the absence of Welsh prevalence and incidence data, the company has adopted a pragmatic approach to estimating the number of eligible patients. However, the Lennox-Gastaut syndrome prevalence estimates are somewhat lower than those adopted in its earlier full submission to AWMSG for rufinamide tablets (269 patients across all age groups)[6], and the revised number of patients estimated to have swallowing difficulties necessitating the use of the oral suspension formulation is lower than originally provided by the company for its limited submission. The

company's estimates of uptake therefore appear subject to uncertainty. The budget impact associated with the use of rufinamide oral suspension is dependent on the alternative use of 400 mg tablets to achieve the required daily dose of rufinamide. The company reports an average daily dose of rufinamide of 1,800 mg (delivered using oral suspension or as a combination of 100 mg and 400 mg tablets). It seems reasonable to assume that in patients requiring lower daily doses of rufinamide that would not require the use of the 400 mg tablet there may be no budgetary impact from the introduction of the oral suspension formulation in NHS Wales. However, it is unclear how frequently this would be the case, as actual doses would need to be individually tailored.

3.3 Comparative unit costs

Table 1. Examples of drug acquisition costs for rufinamide (Inovelon®▼) formulations.

Drug	Example daily dose*	Example annual cost of treatment per patient
Rufinamide (Inovelon®▼) 100 mg, 200 mg, 400 mg oral tablets	1,800 mg/day (2 x 400 mg plus 1 x 100 mg tablets given twice daily)	£2,880
Rufinamide (Inovelon®▼) 40 mg/ml oral suspension	1,800 mg/day (22.5 ml given twice daily)	£3,384
** Company estimate of average daily dose in practice. Note that doses need to be individually tailored based on patient body weight and concomitant antiepileptic treatment.* *Costs are based on MIMS list prices as of 04 May 2012[7].* *See the Summaries of Product Characteristics for licensed indications and full dosing details[2].*		

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, rufinamide (Inovelon®▼) oral suspension is appropriate for prescribing within NHS Wales by specialist recommendation for the indication under consideration.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 25 May 2012
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Eisai Ltd. Form C: Limited appraisal submission. Rufinamide (Inovelon®▼) oral suspension. Apr 2012.

2 Eisai Ltd. Inovelon®▼. Summary of Product Characteristics. Apr 2012. Available at: http://www.medicines.org.uk/EMC/medicine/20165/SPC/Inovelon+Tablets+and+Oral+Suspension/. Accessed May 2012.

3 European Medicines Agency. Inovelon. Procedural steps taken and scientific information after the authorisation. Dec 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000660/WC500032942.pdf. Accessed May 2012.

4 Critchley DJ, Aluri J, Boyd P et al. Bioavailability of three rufinamide oral suspensions compared with the marketed 400-mg tablet formulation: results from a randomized-sequence, open-label, four-period, four-sequence crossover study in healthy subjects. *Clin Ther* 2011; 33 (1): 146-57.

5 European Medicines Agency. Assessment Report for Inovelon. Procedure No.: EMEA/H/C/000660/X/0017. Jan 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000660/WC500120292.pdf. Accessed May 2012.

6 All Wales Medicines Strategy Group. Final Appraisal Recommendation. Advice no. 1708. Rufinamide (Inovelon®▼). Oct 2008. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Rufinamide%20%28Inovelon%29%20FAR%20Final%20For%20Website.pdf. Accessed May 2012.

7 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2012. Available at: http://www.mims.co.uk/. Accessed May 2012.