Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study evaluated the cost-effectiveness of the addition of rufinamide compared with topiramate or lamotrigine for children with Lennox-Gastaut Syndrome that was uncontrolled by up to three traditional antiepileptic drugs, in the UK. The authors concluded that rufinamide was likely to be cost-effective compared with topiramate. There were significant issues with the methods and the conclusions were inappropriate for the evidence presented. Topiramate should not be considered for these patients and rufinamide was unlikely to be cost-effective, compared with lamotrigine.

Type of economic evaluation
Cost-utility analysis

Study objective
To evaluate the cost-utility of rufinamide compared with topiramate or lamotrigine as adjunctive therapy for children with Lennox-Gastaut Syndrome that was not controlled by up to three traditional antiepileptic drugs.

Interventions
The interventions were a daily dose of rufinamide 40.20mg per kg, topiramate 8.3mg per kg, or lamotrigine 5.3mg per kg, as an addition to a mix of up to three traditional antiepileptic drugs, such as valproate, clonazepam, clobazam, carbamazepine, phenytoin and phenobarbitone.

Location/setting
UK/secondary care.

Methods
Analytical approach:
A Markov model with a three-year time horizon was used for the transition between states of percentage reduction in tonic-atonic (drop attack) seizures from baseline. The authors reported a UK NHS and Personal Social Services perspective.

Effectiveness data:
The authors performed an extensive literature search to identify the clinical trial evidence for the included treatments. Three randomised placebo-controlled trials of patients with Lennox-Gastaut Syndrome were identified; one for each drug. An indirect comparison was performed, using a fixed-effect model, to derive the required transition probabilities.

Monetary benefit and utility valuations:
Improvement in quality of life was from a separate study, which estimated it using the time trade-off technique.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs) and a 3.5% annual discount rate was applied.

Cost data:
The cost categories included drug acquisition, treatment of adverse events, and other direct health care (diagnostic procedures, personal social services, and in-patient stay). The sources included the British National Formulary, a survey
of specialist physicians, the Personal Social Services Research Unit, and NHS Reference Costs. All costs were reported in 2006 to 2007 UK pounds sterling (£) and a 3.5% annual discount rate was used.

Analysis of uncertainty:
A probabilistic sensitivity analysis was performed and several one-way sensitivity and scenario analyses were considered.

Results
The total accumulated costs were £24,992 for rufinamide, £23,360 for topiramate, and £21,783 for lamotrigine. The QALYs were 1.44 for rufinamide, 1.36 for topiramate, and 1.42 for lamotrigine. The incremental cost per QALY gained for rufinamide was £20,538 compared with topiramate, and £154,831 compared with lamotrigine.

According to the probabilistic sensitivity analysis, rufinamide was cost-effective compared with topiramate in 65% and lamotrigine in 15% of iterations, at a willingness-to-pay of £30,000 per QALY gained. Alternative scenarios showed similar results to those of the base case analysis. These results were sensitive to the response and maintaining probabilities associated with each drug.

Authors' conclusions
According to the authors, rufinamide was likely to be cost-effective compared with topiramate, as an additional treatment for children with Lennox-Gastaut Syndrome. They stated that rufinamide should be considered as an effective alternative to lamotrigine, given the importance of patient choice and equal access, for such a rare and devastating condition.

CRD commentary
Interventions:
No additional treatment (the mix of traditional antiepileptic drugs alone) was not considered as an initial option, but it was considered following withdrawal due to adverse events. It is possible that none of the interventions were cost-effective compared with traditional antiepileptic drugs. The authors stated that the comparison with lamotrigine was a secondary analysis due to a lack of evidence, but this was not good reason to make the comparison secondary. They also did not explain how the evidence was lacking for this treatment, as the effectiveness parameters reported were more precise for lamotrigine than those for the other treatments.

Effectiveness/benefits:
The literature search was not described. No head-to-head comparisons between the drugs were found and an indirect comparison was made, which seems to have been appropriate. A lifetime horizon was not considered because the authors found no evidence of long-term effectiveness. There was little discussion of the adverse events, which were modelled to occur within the first three months and it was not clear if this was based on evidence from the trials.

Costs:
A micro-costing approach was used and all those costs relevant to the reported perspective seem to have been included. The authors stated that the medical resource costs and the costs of treating adverse events were expected to be lowest with rufinamide, but they did not explain this and rufinamide had the highest cost per day and the highest adverse event rate. The average daily doses for each treatment were the opinions of clinical experts. These could have been tested in a sensitivity analysis, using the doses recommended in their Summary of Product Characteristics.

Analysis and results:
According to the authors’ assumptions, topiramate was dominated by lamotrigine, as lamotrigine was cheaper and more effective, and so it should not be considered as an option for these particular patients. The main comparator for rufinamide was therefore lamotrigine, and rufinamide was unlikely to be cost-effective compared with lamotrigine, at the usual NHS willingness-to-pay threshold. Rufinamide should therefore have limited use as a second-line therapy, such as when lamotrigine cannot be used and an adjunctive therapy is considered necessary. The cost-effectiveness of each treatment compared with no adjunctive treatment was not assessed, meaning that it is possible that rufinamide is never cost-effective. It wasn't clear if distributions were applied to all the parameters for the probabilistic sensitivity analysis. The authors stated that one-way sensitivity analysis was used to test the uncertainty in the model parameters.
by varying them by ±20%; it was unclear how well an arbitrary ±20% represented the uncertainty in each parameter.

Concluding remarks:
There were significant issues with the methods of this analysis and the conclusions were not appropriate for the evidence presented.

Funding
Funding received from Eisai Ltd, manufacturer of rufinamide.

Bibliographic details

PubMedID
19942457

DOI
10.1016/j.seizure.2009.10.003

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Anticonvulsants /economics /therapeutic use; Child; Confidence Intervals; Cost-Benefit Analysis /economics; Drug Utilization /statistics & numerical data; Epilepsy /drug therapy /economics; Follow-Up Studies; Fructose /analogs & derivatives /economics /therapeutic use; Great Britain; Health Status; Humans; Markov Chains; Quality of Life; Sensitivity and Specificity; Triazines /economics /therapeutic use; Triazoles /economics /therapeutic use

AccessionNumber
22010000459

Date bibliographic record published
04/08/2010

Date abstract record published
29/06/2011