CDEC FINAL RECOMMENDATION

RUFINAMIDE
(Banzel – Eisai Limited)
Indication: Lennox-Gastaut Syndrome; Adjunctive Treatment of Seizures

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that rufinamide be listed for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome for patients who meet all of the following criteria:

- Are under the care of a physician experienced in treating Lennox-Gastaut syndrome-associated seizures, and
- Are currently receiving two or more antiepileptic drugs, and
- In whom less costly antiepileptic drugs are ineffective or not appropriate.

Reasons for the Recommendation:

1. In one double-blind randomized controlled trial (RCT) of patients with Lennox-Gastaut syndrome receiving concomitant antiepileptic drugs, rufinamide achieved a statistically significant reduction in the frequency and severity of seizures compared with placebo.

2. The daily cost of rufinamide ($1.58 to $25.04 for 200 mg to 3,200 mg) is significantly greater than the cost of other antiepileptic agents used for this condition; for example, lamotrigine.

Background:
Rufinamide has a Health Canada indication for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children aged four years and older, and adults. The precise mechanism by which rufinamide exerts its antiepileptic effect is unknown. Rufinamide is available as 100 mg, 200 mg, and 400 mg oral tablets.

Treatment with rufinamide should be initiated at a dose of 200 mg per day in patients less than 30 kg, and 400 mg per day in patients 30 kg or greater. According to clinical response and tolerability, the dose should be increased by 5 mg/kg per day every two weeks after an evaluation of efficacy. Titration should be stopped after satisfactory control of seizures is obtained, based on clinical judgment. The maximum daily dose is 1,300 mg per day for patients less than 30 kg, and 3,200 mg per day for patients 30 kg or greater.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of rufinamide, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
One double-blind RCT met the criteria for inclusion in the systematic review. Study 022 (N = 139) compared rufinamide with placebo in children and adults with uncontrolled seizures associated with Lennox-Gastaut syndrome who were using one to three concomitant antiepileptic drugs. The trial consisted of a pre-randomization baseline phase (four weeks), a double-blind titration phase (one to two weeks), a double-blind maintenance phase (10 weeks), and an open-label extension phase (up to 36 months). Patients began treatment with a 10 mg/kg per day dosage, which was subsequently titrated over a 14-day period toward a target of 45 mg/kg per day. Concomitant antiepileptic drugs and doses were to remain fixed throughout the double-blind phase of the trial (i.e., 12 weeks). Total withdrawals were more common with rufinamide compared with placebo (14.7% versus 7.8%). There are currently no studies directly comparing rufinamide with other active antiepileptic drugs for the treatment of seizures associated with Lennox-Gastaut syndrome.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in total and tonic-atonic seizure (i.e., drop attack) frequency, seizure severity, proportion of responders, withdrawal due to adverse events, and adverse events.

Study 022 included three primary efficacy outcomes: 1) percent change from baseline in total seizure frequency per 28 days; 2) percent change from baseline in tonic-atonic seizure frequency per 28 days; and 3) seizure severity rating from the Global Evaluation of the patient's condition. Responders were defined as those patients achieving at least a 50% reduction in seizure frequency per 28 days. Patient group input suggests that reductions in seizure frequency and severity can have a profound impact on the quality of life for patients and their caregivers. However, change in quality of life, using a validated scale, was not measured in study 022.

Results

Efficacy
- Rufinamide-treated patients had a statistically significantly greater median change from baseline in the 28-day total seizure frequency, compared with placebo: -32.7% versus –11.7%, respectively. The decrease in total seizure frequency was significantly greater in the rufinamide group compared with placebo, irrespective of the number or the type of antiepileptic drugs used at baseline.
- Rufinamide-treated patients had a statistically significantly greater median change from baseline in the 28-day tonic-atonic seizure frequency, compared with placebo: -42.5% versus +1.4%, respectively.

- Compared with placebo, a statistically significantly higher proportion of rufinamide-treated patients achieved an improved seizure severity rating: 53.4% versus 30.6%, respectively.
- A statistically significantly higher proportion of patients in the rufinamide group had a reduction in tonic-atonic seizure frequency of at least 50% compared with placebo (42.5% versus 16.7%). Similarly, compared with placebo, a statistically significantly higher proportion of rufinamide-treated patients achieved a reduction in tonic-atonic seizure frequency of at least 25% and at least 75%.
- There were no statistically significant differences in the Global Evaluation Composite Scores between rufinamide and placebo at the end of the double-blind treatment phase.

Harms (Safety and Tolerability)

- Three patients (4.1%) in the rufinamide group experienced a total of nine serious adverse events, and two patients (3.1%) in the placebo group each experienced one serious adverse event. Status epilepticus occurred in three patients in the rufinamide group and no patients in the placebo group.
- At least one adverse event of any severity was reported for 81% of patients in each treatment group. Compared with placebo, patients treated with rufinamide had a numerically higher incidence of nervous system disorders (39.2% versus 23.4%) and skin and subcutaneous tissue disorders (21.6% versus 4.7%).
- Withdrawals due to adverse events were reported for 8.1% of rufinamide-treated patients and 0% of placebo-treated patients.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing rufinamide with lamotrigine or topiramate in combination with other therapies (such as valproate, clonazepam, carbamazepine) for patients with Lennox-Gastaut syndrome over a three-year time horizon. The efficacy at three months for each therapy (i.e., at least 50% and at least 75% reduction in drop attacks) was derived from a mixed treatment comparison (MTC) meta-analysis. After the initial three-month period, the efficacy for each of the treatments was assumed to be equivalent and based on the rufinamide open-label extension of study 022. The utility values for each of the health states were derived from a separate Lennox-Gastaut syndrome study, which reported Time-Trade-Off (TTO) and European Quality of Life — 5 Dimension (EQ-5D) questionnaire derived utilities. The manufacturer reported that rufinamide is associated with an incremental cost per quality-adjusted life-year of $55,715 (based on EQ-5D) and $111,991 (based on TTO) compared with topiramate, and between $127,084 (based on EQ-5D) and $362,127 (based on TTO) compared with lamotrigine.

CDR identified a number of issues with the manufacturer's submission: the results were sensitive to the utility weights used, and no subgroups were considered (all children aged four years and older, and adults), limiting the ability to identify subgroups for which the incremental cost-utility value may be lower.

The daily cost of rufinamide ($1.58 to $25.04 for 200 mg to 3,200 mg) is higher than the daily cost of topiramate ($0.33 to $1.77 for 25 mg to 400 mg) and lamotrigine ($0.15 to $1.87 for 40 mg to 500 mg).

Patient Input Information
The following is a summary of information provided by four patient groups who responded to the CDR Call for Patient Input.

- Patient groups emphasized the difficulty of controlling Lennox-Gastaut syndrome; an additional treatment option is seen as very important for those who are unresponsive to other agents.
- Patient groups indicated that any reduction in the frequency or severity of seizures can have a profound impact on their and their caregivers' quality of life while potentially allowing for greater independence, fewer trips to the emergency room, and greater success in either academic or workplace settings.
- Patient groups stated that patients with Lennox-Gastaut syndrome and their caregivers are affected by a high level of unemployment, which limits access to private drug insurance plans. As a result, they feel it is vitally important that publically funded plans provide funding for new anti-seizure medications.

Other Discussion Points:

- The Committee recognized that Lennox-Gastaut syndrome is an uncommon condition that can be very difficult for patients and caregivers to manage.
- The Committee noted that tonic-atonic seizures (drop attacks) are of particular concern due to the considerable potential for injury.
- The Committee noted that rufinamide is structurally unrelated to other currently available antiepileptic drugs.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

February 15, 2012 meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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