Advances in Epilepsy Treatment
New and Emerging AEDs

July 5, 2011
Raman Sankar, MD, PhD
David Geffen School of Medicine at UCLA
Los Angeles, California
Recent & Anticipated Approvals

- Lacosamide (Vimpat – UCB)
- Rufinamide (Banzel – Eisai)
- Ezogabine (Potiga – Valeant + GSK)
- Eslicarbazepine (Stedesa – Sunovion)
- Perampanel (Eisai)
- Brivaracetam (Rikelta – UCB)
VIMPAT® tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years.

VIMPAT® injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years when oral administration is temporarily not feasible.
Lacosamide: The Molecule

- Functionalized amino acid (Glycine derivative)
- R(+) configuration is active
- Molecular weight: 250.3 g/mol
- Aqueous solubility: ~25

Physiology of Voltage-Gated Sodium Channels

Regulation of sodium channel long-term availability

Local anesthetics

Classical AEDs

Resting state

Repolarization

Inactivated state-fast (within msec)

Inactivated state-slow (within sec and beyond)

Open state

LCM Selectively enhances slow inactivation


msec=milliseconds; Na+=sodium; sec=seconds
Pharmacokinetic Properties

- Dose proportionality of $C_{\text{max}}$ and AUC
- Low inter- and intra-subject variability of about 20%
- $T_{\text{max}}$ between 1 and 4 hours after oral administration
- $T_{1/2}$ ~13 hours
- High oral bioavailability of approximately 100%
- 95% of the dose is excreted in the urine
- Volume of distribution ~0.65 l/kg
- Low protein binding (<15%)
- Bioequivalence of oral and iv (30- and 60-minute infusion)

AUC=area under plasma concentration–time curve; $C_{\text{max}}=$maximum observed plasma concentration; iv=intravenous; $T_{1/2}=$plasma terminal elimination half-life; $T_{\text{max}}=$time to $C_{\text{max}}$
Plasma Concentrations Are Proportional After Single Dose Administration

*600 mg and 800 mg/d are above the approved maximum dose

UCB data on file: Summary Clinical Pharmacology p8–9.
Lacosamide Demonstrates Efficacy with a Broad Range of AEDs

≥50% Responder Rate from Baseline*

*Per 28 days from baseline to maintenance. Intent-to-treat population. Most patients were taking >1 AED; therefore, these groups may not be mutually exclusive.

Data on file; UCB, Inc. Rosenfeld W, et al. Poster presented at: 62nd Annual American Epilepsy Society Meeting; December, 5-9, 2008; Seattle, WA. Please see your UCB sales representative for full prescribing information.
Drug-Drug Interaction Trials

- In drug–drug interaction trials, no clinically significant PK interaction has been observed with:
  - Carbamazepine*
  - Valproic acid
  - Omeprazole (inhibitor of CYP2C19)
  - Ethinylestradiol and levonorgestrel
  - Metformin
  - Digoxin

*Available Population PK data indicate that the plasma concentrations of lacosamide may be decreased under concomitant treatment with carbamazepine, phenytoin, and phenobarbital. The influence is considered of minor clinical relevance and no dose adjustment is necessary.
PK=pharmacokinetic; PopPK=population pharmacokinetic analysis

Horstmann RP, et al. Presented at AES.
Drug-Drug Interaction Profile with Marketed AEDs

<table>
<thead>
<tr>
<th>AED co-administered</th>
<th>Dose AED [mg/day]</th>
<th>Influence of LCM* on AED</th>
<th>Influence of AED on LCM*</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>1000–2200</td>
<td>No</td>
<td>No</td>
<td>SP586</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>400</td>
<td>No</td>
<td>No</td>
<td>SP586</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600–2400</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200–3600</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>100–1200</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000–5000</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>900–3600</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>200–700</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>300–700</td>
<td>No</td>
<td>No</td>
<td>SP607</td>
</tr>
</tbody>
</table>

*200–600 mg/day,
SP586= multicenter, uncontrolled, ascending-dose trial to evaluate the tolerability, compatibility, efficacy and PK of LCM as add-on therapy in patients with POS
SP607= multicenter, open-label, single-arm, dose-titration trial to determine the maximum tolerated dose of LCM (<600 mg/day) and evaluate efficacy of LCM as add-on therapy in patients with POS
AEDs= antiepileptic drugs; LCM= lacosamide; POS= partial-onset seizure

### Treatment-Emergent Adverse Events (Frequency ≥10% During Treatment Phase): Titration Vs. Maintenance

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Titration (%)</th>
<th>Maintenance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=364</td>
<td>Total Lacosamide n=944</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Coordination Abnormal</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Injection: Dosing and Administration

- 200 mg of VIMPAT®/20 mL single-use vial
  - Concentration: 10 mg/mL
  - pH: 3.5-5.0*

- Does not require additional dilution prior to administration or may be mixed with diluents
  - Compatible and stable with sodium chloride injection 0.9% (w/v), dextrose injection 5% (w/v), and lactated Ringer’s injection

- Store at room temperature

- **Infusion rate: At least 30 minutes**

- 1:1 dose conversion (oral ↔ injection)

*Hydrochloric acid is used for pH adjustment.*
Summary of Efficacy and Safety of Lacosamide

- LCM at doses of 200, 400 and 600 mg/day significantly reduced seizure frequency despite 1–3 concomitant AEDs
- LCM use was generally well tolerated and was associated with dose-related CNS and GI adverse events
- No clinically relevant influence of LCM on laboratory results, vital signs, ECG, or body weight was recorded
- Caution – when used with drugs that prolong PR interval – syncope risk. (e.g.) β-blockers, procainamide, quinidine, digitalis, verapamil, mexiletine, et cetera
3 patients with LGS, mid-twenties

Tonic seizures increased in each, including when awake – no benefit in other types

One experienced tonic status for 6 hours
Case report

Successful treatment of refractory simple motor status epilepticus with lacosamide and levetiracetam

Leo L.K. Chen\textsuperscript{a, b, *}, Zulfi Haneef\textsuperscript{a}, Andrew Dorsch\textsuperscript{a}, Inna Keselman\textsuperscript{a}, John M. Stern\textsuperscript{a}

\textsuperscript{a}David Geffen School of Medicine at UCLA, Neurology, Los Angeles, CA, United States
\textsuperscript{b}VA Greater Los Angeles Health Care System, Neurology, Los Angeles, CA, United States
The success rate in patients receiving LCM as first or second drug was 3/5, as third drug 11/19, and as fourth or later drug 3/15. In five subjects, SE could not be terminated at all. No serious adverse events attributed to LCM were documented.

**Conclusions** Intravenous LCM may be an alternative treatment for established SE after failure of standard therapy, or when standard agents are considered unsuitable.
Rufinamide (Banzel™- Eisai)
<table>
<thead>
<tr>
<th>AED</th>
<th>Rotorod test</th>
<th>MES test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TD&lt;sub&gt;50&lt;/sub&gt; (95% CI)</td>
<td>ED&lt;sub&gt;50&lt;/sub&gt; (95% CI)</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>&gt;500 (95% CI)</td>
<td>15.5 (12.5–18.1)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>65.5 (52.5–72.1)</td>
<td>9.5 (8.1–10.4)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>69.0 (62.8–72.9)</td>
<td>21.8 (15.0–25.5)</td>
</tr>
<tr>
<td>Valproate</td>
<td>425.8 (369–450)</td>
<td>272 (247–338)</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>440.8 (383–485)</td>
<td>1,000 no protection</td>
</tr>
</tbody>
</table>
Rufinamide’s protective index exceeds that of PHT in the MES test and that of ethosuximide and VPA in the PTZ test, suggesting a broad spectrum of action; MOA remains unclear – Na⁺ channel antagonism has been demonstrated but may involve other mechanisms.

White SH et al., *Epilepsia*, 2008
**Pharmacokinetics**

- **Absorption**
  - Well absorbed after oral administration
  - At higher dose, dose-limited due to limited solubility
- **Distribution**
  - 34% protein binding (27% to albumin)
- **Metabolism**
  - Extensively metabolized through carboxylesterase(s) mediated hydrolysis
  - None of metabolites have anti-seizure activity
  - BANZEL™ (rufinamide) is slight inducer of CYP 4503A4 enzyme
- **Elimination/Excretion**
  - $T_{\text{max}} = 4$–6 hours
  - Half-life = 6–10 hours
  - Renal excretion was predominant route of elimination (85%)
- **No significant difference of PK profile as a function of age**
  - Ages 4 to 80 years


BANZEL™ (rufinamide) Prescribing Information.
## Dosage and administration (in clinical trials)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial dosage</th>
<th>Maximum dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>10 mg/kg/day</td>
<td>45 mg/kg/day</td>
</tr>
<tr>
<td>Partial Seizures</td>
<td>200–1600 mg/day</td>
<td>3200 mg/day</td>
</tr>
</tbody>
</table>

Route of administration: Oral

### Pharmacokinetic profile (after a single oral 400mg dose in healthy adult volunteers)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maximum plasma concentration ($C_{max}$)</td>
<td>3.03 µg/mL</td>
</tr>
<tr>
<td>Mean area under the plasma concentration-time curve from 0 to 48 hours</td>
<td>49.4 µg • h/mL</td>
</tr>
<tr>
<td>Mean time to $C_{max}$</td>
<td>6.56h</td>
</tr>
<tr>
<td>Mean elimination half-life</td>
<td>8.82h</td>
</tr>
</tbody>
</table>

### Most frequent adverse events (incidence ≥10%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>Somnolence, vomiting</td>
</tr>
<tr>
<td>Partial seizures (pooled data)</td>
<td>Headache, dizziness, fatigue, nausea, somnolence, diplopia</td>
</tr>
</tbody>
</table>

a It should be noted that the upper limit recommendation for the initial rufinamide dosage will be lower than 1600 mg/day.
Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome

ABSTRACT

Background: Lennox–Gastaut syndrome is a catastrophic pediatric epilepsy syndrome characterized by multiple types of treatment-resistant seizures and high rates of seizure-related injury. Current available treatments are inadequate, leaving patients with few treatment options and opportunities.

Methods: We conducted a double-blind, randomized, placebo-controlled trial of the antiepileptic
Table 1  Rufinamide dosing schedule

<table>
<thead>
<tr>
<th>Trial day (titration phase)</th>
<th>Approximate dose (mg/kg/d)</th>
<th>Actual dose by body weight (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>18.0-29.0 kg</td>
</tr>
<tr>
<td>1-2</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>3-4</td>
<td>20</td>
<td>400</td>
</tr>
<tr>
<td>5-6</td>
<td>30</td>
<td>800</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>1,000</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Rufinamide (n = 74)</td>
<td>Placebo (n = 64)</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (62.2)</td>
<td>40 (62.5)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (37.8)</td>
<td>24 (37.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62 (83.8)</td>
<td>53 (82.8)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (8.1)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (8.1)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>13.0 (4.0-35.0)</td>
<td>10.5 (4.0-37.0)</td>
</tr>
<tr>
<td>4–&lt;12, n (%)</td>
<td>31 (41.9)</td>
<td>33 (51.6)</td>
</tr>
<tr>
<td>12–&lt;17, n (%)</td>
<td>19 (25.7)</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>≥17, n (%)</td>
<td>24 (32.4)</td>
<td>14 (21.9)</td>
</tr>
</tbody>
</table>
Rufinamide in LGS

Figure 2  Median percentage reduction in total seizure frequency and tonic-atonic seizure frequency (per 28 days during the double-blind phase relative to baseline)

- Rufinamide: 42.5% reduction, p < 0.0001
- Placebo: 32.7% reduction, p = 0.0015

Figure 3  Percentage of patients (responders) who experienced at least a 50% reduction in tonic-atonic and total seizure frequency (per 28 days during the double-blind phase relative to baseline)

- Rufinamide: 42.5% responders, p = 0.002
- Placebo: 31.1% responders, p = 0.0045

Glauser T et al, Neurology, 2008
Long-term efficacy of Rufinamide in Lennox-Gastaut Syndrome

Deeks & Scott, *CNS Drugs*, 2006
## AED Drug Interactions

<table>
<thead>
<tr>
<th>AED Co-administered</th>
<th>Influence of BANZEL™ (rufinamide) on AED Concentration</th>
<th>Influence of AED on BANZEL (rufinamide) Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Decrease by 7 to 13%</td>
<td>Decrease by 19 to 26% Dependent on dose of carbamazepine</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Decrease by 7 to 13%</td>
<td>No Effect</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Increase by 8 to 13%</td>
<td>Decrease by 25 to 46% Independent of dose or concentration of phenobarbital</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increase by 7 to 21%</td>
<td>Decrease by 25 to 46% Independent of dose or concentration of phenytoin</td>
</tr>
<tr>
<td>Topiramate</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Valproate</td>
<td>No Effect</td>
<td>Increase by &lt; 16 to 70% Dependent on concentration of valproate</td>
</tr>
<tr>
<td>Primidone</td>
<td>Not Investigated</td>
<td>Decrease by 25 to 46% Independent of dose or concentration of primidone</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Not Investigated</td>
<td>No Effect</td>
</tr>
</tbody>
</table>

- Patients stabilized on BANZEL (rufinamide) before being prescribed valproate should begin valproate therapy at a low dose and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a BANZEL (rufinamide) dose lower than 400 mg.
- The effects of BANZEL (rufinamide) on the PK of other AEDs are unlikely to have clinical significance.
- Potent P450 enzyme inducers appear to increase the clearance of BANZEL (rufinamide).

BANZEL™ (rufinamide) Prescribing Information.
The Effect of the New Antiepileptic Drug Rufinamide on Cognitive Functions

*†Albert P. Aldenkamp and ‡Willem C. J. Alpherts

*Department of Behavioural Sciences Epilepsy Centre Kempenhaeghe, Heeze; †Department of Neurology, Maastricht University Hospital, Maastricht; and ‡Department of Psychology ‘SEIN, Heemstede, The Netherlands

Conclusions: RUF is a new AED with no serious cognitive effects even in add-on treatment and even in the higher dose ranges.
The Possible Antianxiety and Mood-Stabilizing Effects of Rufinamide

Maurizio Fava

Depression Clinical and Research Program, Massachusetts General Hospital, Boston, Mass., USA
Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study


The Cost Effectiveness of Rufinamide in the Treatment of Lennox-Gastaut Syndrome in the UK

Ágnes Benedict,¹ Lara Verdián² and Grant Maclaine²
Pharmacoeconomics 2010; 28 (3): 185-199
Retigabine
Ezogabine

US FDA Approval granted June 2011
Ezogabine - Potiga® (Valeant-GSK)
US FDA Approval granted June 2011
Figure 1. BFNS- and PNH-causing mutations in KV7.2 and KV7.3 subunits

Antiepileptogenic and antiictogenic effects of retigabine under conditions of rapid kindling: An ontogenic study

*Andréy Mazarati, †Jim Wu, *Don Shin, ‡Young Se Kwon, and §Raman Sankar
Ezogabine Pharmacokinetics

- Extensive first-pass metabolism
- Protein binding about 80%
- Hydrolysis – acetylation & glucuronidation
- N-acetyl not especially active
- Clearance increased by PB, CBZ
- Not so much by VPA, LTG, TPM
Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy

A  Median percent reduction from baseline in 28-day seizure frequency

B  Responder rate (≥50% reduction in total partial-seizure frequency from baseline; ITT population)

12-week maintenance phase

18-week treatment period

**Placebo** (n=152) | **EZG(RTG) 1200 mg/day** (n=153) | **Placebo** (n=137) | **EZG(RTG) 1200 mg/day** (n=119)
---|---|---|---
Median reduction (%) | 17.5 | 44.3 | 18.9 | 54.5 | 17.8 | 44.4 | 22.6 | 55.5

p<0.001
Phase III Trials: Overview

- Two Phase III studies with similar design
  - Randomized, double-blind, placebo-controlled
  - Adult patients with refractory partial-onset seizures on a stable regimen of 1-3 background AEDs
  - Primary endpoints and study design meet US and European regulatory guidance

- Study 302 (RESTORE 2):
  - 600 and 900 mg/day RTG vs placebo

- Study 301 (RESTORE 1):
  - 1200 mg/day RTG vs placebo
Patients with \( \geq 50\% \) Seizure Reduction During Maintenance

*\( p < 0.001 \)
Fisher’s exact test
Responder Rate Over Time by Duration of Retigabine Open-Label Exposure (Study 304)

% Patients with ≥50% Seizure Reduction

% Patients

Treatment Duration, Months

- 12 Months (n=55)
- 9 Months (n=122)
- 6 Months (n=163)
- 3 Months (n=233)
Discontinuations Due to Adverse Events

- Adverse event as primary reason for discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=331)</th>
<th>RTG (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>900</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>1200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Cause for discontinuation in >3% of patients
  - Dizziness*
  - Confusion*
  - Somnolence
  - Fatigue

*Dose-related
Conclusions

- All doses met primary efficacy endpoints
  - Statistically superior to placebo ($p<0.01$) at all doses
  - Clear dose-response established
- Generally well-tolerated
  - Adverse events mostly dose-related
  - Extensive safety experience
- Validates novel mechanism of action
- An important advance for epilepsy patients with refractory partial-onset seizures
- Requires TID dosing
- Even with that 26% discontinued at 900 mg/d
- However, even 600 mg/d met efficacy criteria
- Will need to explore usage strategy for optimizing results
Eslicarbazepine
Stedesa™ - Sunovion
Oxcarbazepine

Eslicarbazepine
Pharmacokinetics

- Peak concentration: 2-3 hrs after dose
- Low protein binding (<40%)
- Bioavailability >90%
- Rapid conversion to eslicarbazepine
- Excretion: 2/3 free; 1/3 as glucuronide
- Effective half life close to 20 hrs
- Steady state reached in 4-5 days
1. In in vitro studies in human liver microsomes, eslicarbazepine had no relevant inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4 and CYP2C9, and only a moderate inhibitory effect on CYP2C19.

2. No significant induction of CYP1A2, CYP3A and phase II enzymes involved in the glucuronidation and sulfatation.

3. No meaningful PK interaction with PHT or LTG.
Efficacy and safety of eslicarbazepine acetate

A

<table>
<thead>
<tr>
<th>Dose</th>
<th>Responder's rate (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>400 mg</td>
<td>23%</td>
<td>n.s.</td>
</tr>
<tr>
<td>800 mg</td>
<td>34%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>1200 mg</td>
<td>43%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Dose</th>
<th>Responder's rate (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>400 mg</td>
<td>25%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>800 mg</td>
<td>32%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>1200 mg</td>
<td>38%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Effect of eslicarbazepine acetate and oxcarbazepine on cognition and psychomotor function in healthy volunteers

Denise Milovan a, Luis Almeida b,c, Myroslava K. Romach a, Teresa Nunes b, José Francisco Rocha b, Marta Sokowloska a, Edward M. Sellers a, Patrício Soares-da-Silva b,d,*

- Two single-blind studies following single and repeated administration in healthy volunteers.
- The cognitive and psychomotor evaluation consisted of several computerized and paper-and-pencil measures.
- ESL and OXC had similar overall cognitive profiles and did not cause clinically relevant cognitive impairment.
- Incidence of adverse events lower with ESL than with OXC.
Eslicarbazepine – Advantages?

- Once daily administration
- Possibly fewer adverse effects than OXC
- Incidence of hyponatremia may be lower
- May not exacerbate PGE compared to CBZ or PHT (???? Unpublished animal data)
- Many of the above will need validation in extended clinical use
Perampanel
The Curious Recent History of AMPA-blockers

- **Talampanel**
- **Studied by Teva in failed studies for:**
  - Malignant gliomas
  - Amyotrophic Lateral Sclerosis
- **Perampanel**
- **Studied by Eisai for Parkinson disease** failed
- **Epilepsy studies? US & Europe vs. Latin America**
Revisiting AMPA Receptors as an Antiepileptic Drug Target

Michael A. Rogawski
Talampanel
Perampanel
Perampanel

- Rapid absorption
- Protein binding about 95%
- Half-life estimated at 70 hrs
- Once daily administration feasible
- Metabolism: hydroxylation by CYP3A4 and glucuronidation
Perampanel Trials

- Phase II studies at 2, 4, 8, 10, and 12 mg/d
- Tolerated with some CNS side effects
- Phase III studies positive in US and Europe
- Did not differentiate in Latin American studies
- FDA submission expected this Summer
Brivaracetam

Rikelta™ - UCB
Levetiracetam

Brivaracetam

Seletracetam
SV2A - a disease-relevant target for AEDs

A. Normal "Wild-type" synapsa: Vesicular release of neurotransmitter

SV2A in synaptic vesicle wall

SV2A

Vesicle Lumen

Neuron Cytoplasm

Brivaracetam

\[
\text{pIC}_{50} \text{ hSV2A}
\]

\[
\text{pED}_{50} \text{ Audiogenic Seizures in Mice}
\]

\[
\text{r}^2 = 0.84
\]

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Adapted from Lynch et al, PNAS 2004; 101:9861-6.
## Mechanism of Action

<table>
<thead>
<tr>
<th>Protein/Current</th>
<th>Effect</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV2A (pKi)</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Na(^+) channel current</td>
<td>7</td>
<td>(~65%)</td>
</tr>
<tr>
<td>(IC(_{50}) value [µM] and max. effect [%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVA Ca(^{2+}) channel current</td>
<td>No effect</td>
<td>up to 1 mM</td>
</tr>
<tr>
<td>(IC(_{50}) value [µM])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVA Ca(^{2+}) channel current</td>
<td>No effect</td>
<td>up to 1 mM</td>
</tr>
<tr>
<td>(IC(_{50}) value [µM])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA &amp; glycine currents</td>
<td>No effect</td>
<td>up to 100 µM</td>
</tr>
<tr>
<td>(IC(_{50}) value [µM])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA/Glycine Zn(^{2+}) inhibition</td>
<td>0.1-1 µM</td>
<td></td>
</tr>
</tbody>
</table>
## Epilepsy pharmacology

<table>
<thead>
<tr>
<th>Models</th>
<th>ED50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute seizure</td>
<td></td>
</tr>
<tr>
<td>MES (mice)</td>
<td>113</td>
</tr>
<tr>
<td>PTZ (mice)</td>
<td>30</td>
</tr>
<tr>
<td>Partial epilepsy</td>
<td></td>
</tr>
<tr>
<td>6 Hz, 44 mA (mice)</td>
<td>4.4</td>
</tr>
<tr>
<td>Amygdala kindling (rats)</td>
<td>44</td>
</tr>
<tr>
<td>Corneal kindling (mice)</td>
<td>1.2</td>
</tr>
<tr>
<td>Generalized epilepsy</td>
<td></td>
</tr>
<tr>
<td>Audiogenic Seizures (mice)</td>
<td>2.4</td>
</tr>
<tr>
<td>GAERS</td>
<td>2.6</td>
</tr>
<tr>
<td>Other models</td>
<td></td>
</tr>
<tr>
<td>Post-hypoxic seizures/myoclonus (rats)</td>
<td>Abolished at 0.3 mg/kg</td>
</tr>
<tr>
<td>SSSE (rats)</td>
<td>Sz duration/cumulative sz time &lt;5%of controls at 100 mg/kg</td>
</tr>
</tbody>
</table>

References:
- Matagne et al, Br J Pharmacol 2008
- Tai and Truong, J Neural Transm 2007
- UCB SA, Data on File
Pharmacokinetics: absorption / distribution

Absorption
- **High bioavailability (~100%)** with $T_{\text{max}} < 2$hrs
- $T_{\text{max}}$ delayed / $C_{\text{max}}$ reduced with high fat meal, **no change in AUC**
- Linear PK across and beyond the therapeutic dose range

Distribution
- Volume of distribution close to total body water (0.52 l/kg)
- Plasma protein binding <20%

---

Sargentini-Maier et al, Drug Metab Dispos 2008
### Major metabolic pathways

<table>
<thead>
<tr>
<th>Urinary metabolites (% dose in 48 h)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent</strong></td>
<td>9%</td>
</tr>
<tr>
<td><strong>Acid/conjugates</strong></td>
<td>38% inactive</td>
</tr>
<tr>
<td>ω-hydroxy</td>
<td>16% inactive</td>
</tr>
<tr>
<td>Hydroxy-acid</td>
<td>15% inactive</td>
</tr>
<tr>
<td>Keto</td>
<td>3.5% active</td>
</tr>
<tr>
<td><strong>Total identified</strong></td>
<td>89%</td>
</tr>
<tr>
<td><strong>Total radiocarbon</strong></td>
<td>92%</td>
</tr>
</tbody>
</table>

**Diagram:**
- **Unchanged Drug**
- **ω-hydroxy**
- **Hydroxy-acid**
- **Keto**
- **Hydrolysis**

**Legend:**
- CYP 2C8
- 1[O]

**References:**
- Sargentini-Maier et al, Drug Metab Dispos 2008
Phase II Data
French et al. *Neurology* 2011
Phase II Data

French et al *Neurology* 2011

**Table 3** Overall summary of TEAEs and TEAEs reported by ≥5% of patients in any treatment group (ITT population)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 54)</th>
<th>BRV5 (n = 50)</th>
<th>BRV20 (n = 52)</th>
<th>BRV50 (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 TEAE</td>
<td>29 (53.7)</td>
<td>26 (52.0)</td>
<td>29 (55.8)</td>
<td>28 (53.8)</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>12 (22.2)</td>
<td>7 (14.0)</td>
<td>10 (19.2)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (7.4)</td>
<td>4 (8.0)</td>
<td>2 (3.8)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 (7.4)</td>
<td>1 (2.0)</td>
<td>3 (5.8)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (7.4)</td>
<td>4 (8.0)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (5.6)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (3.7)</td>
<td>0</td>
<td>2 (3.8)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1.9)</td>
<td>4 (8.0)</td>
<td>2 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
</tbody>
</table>
Brivaracetam does not alter spatial learning and memory in both normal and amygdala-kindled rats


Epilepsia, 52(2):264–272, 2011
doi: 10.1111/j.1528-1167.2010.02746.x

FULL-LENGTH ORIGINAL RESEARCH

Neurocognitive effects of brivaracetam, levetiracetam, and lorazepam

*Kimford J. Meador, †Alan Gevins, ‡Philip T. Leese, §Christian Otoul, and *David W. Loring

*Neurology, Emory University, Atlanta, Georgia, U.S.A.; †San Francisco Brain Research Institute and SAM Technology, San Francisco, California, U.S.A.; ‡Quintiles, Overland Park, Kansas, U.S.A.; and §UCB Pharma, Braine-l’Alleud, Belgium
Conclusions

- In placebo controlled dose ranging studies in patients with refractory partial onset seizures brivaracetam has demonstrated very potent antiepileptic activity.
- Phase II studies suggest 50 mg/d as the optimal dose.
- A drug-drug interaction potential exists across the tested dose range.
- BRV was well tolerated in the potential therapeutic dose-range.
  - Low drop-out rate.
  - AE rates on BRV not significantly different from placebo.
- A phase 3 program with BRV as adjunctive therapy in patients with refractory partial onset seizures is ongoing.
New and Pipeline AEDs

- Of the AEDs discussed, many involve novel compounds and targets
- Others in the pipeline include variations of the old – new versions of CBZ, VPA, etc.
- Some “hiccups” in recent Phase III studies may reflect trends in studies more than the intrinsic properties of compounds