# ESLICARBAZEPINE ACETATE: A WELL-KEPT SECRET?

**Efficacy and Safety of Eslicarbazepine Acetate as Adjunctive Treatment in Adults with Refractory Partial-Onset Seizures: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase III Study.** Elger C, Halász P, Maia J, Almeida L, Soares-da-Silva P, BIA-2093-301 Investigators Study Group. *Epilepsia* 2009;50(3):454–463. PURPOSE: To study the efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in adults with ≥4 partial-onset seizures (simple or complex, with or without secondary generalization) per 4 weeks despite treatment with 1–2 antiepileptic drugs (AEDs). METHODS: This multicenter, parallel-group study had an 8-week, single-blind, placebo baseline phase, after which patients were randomized to placebo ($n = 102$) or once-daily ESL 400 mg ($n = 100$), 800 mg ($n = 98$), or 1,200 mg ($n = 102$) in the double-blind treatment phase. ESL starting dose was 400 mg; thereafter, ESL was titrated at weekly 400-mg steps to the full maintenance dose (12 weeks). RESULTS: Seizure frequency adjusted per 4 weeks over the maintenance period (primary endpoint) was significantly lower than placebo in the ESL 1,200-mg ($p = 0.0003$) and 800-mg ($p = 0.0028$) groups [analysis of covariance (ANCOVA) of log-transformed seizure frequency]. Responder rate was 20% (placebo), 23% (400 mg), 34% (800 mg), and 43% (1,200 mg). Median relative reduction in seizure frequency was 16% (placebo), 26% (400 mg), 36% (800 mg), and 45% (1,200 mg). The most frequent concomitant AEDs were carbamazepine (56–62% of patients), lamotrigine (25–27%), and valproic acid (22–28%). Similar efficacy results were obtained in patients administered ESL with or without carbamazepine as concomitant AED. Discontinuation rates caused by adverse events (AEs) were 3.9% (placebo), 4% (400 mg), 8.2% (800 mg), and 19.6% (1,200 mg). AEs in >10% of any group were dizziness, headache, and diplopia. Most AEs were mild or moderate. DISCUSSION: ESL, 800 and 1,200 mg once-daily, was well tolerated and more effective than placebo in patients who were refractory to treatment with one or two concomitant AEDs.

## COMMENTARY

Eslicarbazepine acetate is a third generation, single enantiomer member of the commonly prescribed first-line dibenz[*b,f*]azepine family of antiepileptic drugs (AEDs), which includes carbamazepine (first generation) and oxcarbazepine (second generation) (1,2). Eslicarbazepine acetate was developed by scientists in Portugal approximately 10 years ago (2,3). While oxcarbazepine is metabolized to both R- and the S-licarbazepine, as well as being detectible in serum as the parent compound, eslicarbazepine acetate is rapidly converted, primarily to S-licarbazepine (also known as eslicarbazepine), and is generally undetectable in serum as the parent compound. The development of eslicarbazepine acetate was based on the view that S-licarbazepine would be a more effective component, have fewer adverse effects, and cross the blood brain barrier more efficiently than R-licarbazepine. Similar to oxcarbazepine, a main distinction between eslicarbazepine acetate and carbamazepine is that eslicarbazepine lacks a toxic epoxide.

After Phase III trials were completed (mainly carried out in Europe and South America), eslicarbazepine acetate was approved by the European Medicines Agency (EMEA) and will soon be available in most European countries as adjunct therapy for adult patients with refractory partial seizures. Clinical trials have started in the United States, and the FDA accepted a new drug approval submission in March 2009 (which also was for adjunct therapy for adults with partial onset seizures); at the time of submission of this article, drug approval had not been determined.

The metabolism of eslicarbazepine acetate consists primarily of hydrolysis to eslicarbazepine (S-licarbazepine), and it is subject to glucuronidation (its main metabolic pathway), followed by renal excretion. In total, eslicarbazepine acetate and its glucuronide conjugates correspond to 92% of the total drug material excreted in urine (3).

Eslicarbazepine acetate has minimal interaction with the cytochrome P450 liver enzymes, thereby decreasing the risk for drug–drug interactions compared to carbamazepine and oxcarbazepine. In in vitro studies of human liver microsomes, eslicarbazepine acetate appeared to have no relevant inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4, or CYP2C9 and only a moderate inhibitory effect on CYP2C19 (1,3). There are no significant effects on digoxin pharmacokinetics, *R*-warfarin pharmacokinetics (mainly metabolized by CYP3A4 substrate), coagulation, or metformin pharmacokinetics (3). Because the half-life of

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eslicarbazepine is 13 to 20 hours in patients on concomitant AEDs, the drug was tested for once-daily dosing in the clinical trials.

Publications of the trial outcomes generally are lagging behind the approval process. One Phase II study was published in 2007 (4), and the randomized, controlled trial comparing eslicarbazepine acetate with placebo reviewed here is the first of three Phase III papers to be published. Results of this study demonstrated very promising efficacy and tolerability to the drug given once daily, even among patients taking combinations of other AEDs, including approximately 60% who were also on carbamazepine. However, no patient in the study was being administered oxcarbazepine because of the similarity of the metabolites.

Why is this drug distinctive and what are the features that make it noteworthy? Eslicarbazepine acetate appears to have a more favorable profile than its relative's carbamazepine and oxcarbazepine. With a once-daily dosing schedule, it appears to have the efficacy features but not the adverse side effects that so often plague patients taking oxcarbazepine and carbamazepine. In retrospective analysis over a 5-year period, hyponatremia (<125 mmol/L) was found in 9.2% of the patients taking oxcarbazepine (5). Hyponatremia occurred rarely with eslicarbazepine acetate in the Elger et al. study, presented here. Although the Elger et al. trial occurred over a much shorter 12-week period than the oxcarbazepine study, during the double-blind treatment phase, only one patient taking 800 mg of eslicarbazepine (<1%) had hyponatremia. While obviously not a head-to-head comparison, the difference in prevalence rates is an issue that warrants further investigation. In addition, the rate of rash incidences was very low, even when eslicarbazepine acetate was taken concomitantly with carbamazepine. Rash occurred in only three patients receiving the study drug (1%) as well as in one patient on placebo. In the SANAD study, which evaluated the efficacy and tolerability of monotherapy drugs for patients with new onset epilepsy, the rash rate for oxcarbazepine was 6% and 7% for carbamazepine (6). The reduced rates of rash and hyponatremia associated with eslicarbazepine acetate will benefit patients, especially given that carbamazepine and oxcarbazepine are currently considered the gold standard drugs to treat partial seizures (7).

Cognitive and psychiatric side effects associated with eslicarbazepine acetate were few, which is also a leap forward in treatment of patients with epilepsy. In this study, among 402 randomized subjects on the drug, psychiatric side effects occurrences were: anxiety in one, depression in one, insomnia in three, and irritability in two patients. In the long-term follow-up of patients enrolled in the double-blind studies, there was no indication of depression or other cognitive side effects, hyponatremia, or rash developing during an observation period of 1 year (8).

What can the future hold for eslicarbazepine acetate? Indeed, if the results of the controlled trials persist in the general epilepsy population with partial onset seizures, then eslicarbazepine may not only be used as an add-on drug for refractory patients with partial onset seizures but may in some cases replace carbamazepine and oxcarbazepine in less the severely affected population, affording patients easier use and fewer side effects, while enjoying the same or better efficacy. Naturally, more clinical trial results are necessary in order to determine the value of eslicarbazepine and to establish just how effective and useful this drug will be in the clinic.

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