**Eslicarbazepine Acetate Drug-Drug Interactions: Characterization Through a Model-Based Population Approach**

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**Objectives:** A population model-based characterization of drug-drug interactions (DDI) was conducted to assess whether potential interactions of antiepileptic drugs (AEDs) used concomitantly with eslicarbazepine acetate (ESL, Aptiom) to treat partial-onset seizures (POS) had a clinically significant effect on eslicarbazepine (primary active metabolite) pharmacokinetics (PK).

**Methods:** DDI with AEDs were evaluated in Phase I studies of ESL 1200 mg QD co-administered with lamotrigine, topiramate, phenytoin and carbamazepine. Pooled PK data from three Phase III trials of ESL (400-1200 mg) coadministered with carbamazepine, phenobarbital, phenytoin, levetiracetam, gabapentin, or valproate were also characterized through a population approach. The effects of AEDs on apparent eslicarbazepine clearance (CL/F) and exposure and ESL on CL/F and exposure to other AEDs were evaluated.

**Results:** In Phase I studies, co-administration of ESL decreased the exposure to lamotrigine (14%), topiramate (18%), and carbamazepine (10%); and increased the exposure to phenytoin (35%). In the same subjects, lamotrigine, topiramate, carbamazepine, and phenytoin decreased the exposure to eslicarbazepine by 4%, 7%, 32%, and 33%, respectively. In the population pharmacokinetic analyses, a one-compartment model with first-order absorption and linear elimination described eslicarbazepine pharmacokinetics; for other AEDs, population models were developed to estimate apparent oral clearance. Coadministration of ESL and carbamazepine resulted in decreased exposure to both carbamazepine (4-10%) and eslicarbazepine (25-34%). Eslicarbazepine exposure decreased (34%) in presence of phenobarbital and similar metabolic inducers including phenytoin and primidone. No clinically relevant change in exposure was seen in the remaining AEDs studied (Figure 1).
Conclusions: In these studies, no clinically relevant DDIs were observed when ESL was co-administered with levetiracetam, gabapentin, lamotrigine, topiramate, phenobarbital, or valproate, therefore, no dose adjustment of these AEDs or ESL is anticipated. In contrast, co-administration of carbamazepine, phenytoin and phenobarbital led to potentially clinically meaningful reductions in eslicarbazepine exposure. The dose of ESL may need to be increased and should be guided by both pharmacokinetic and clinical response considerations. Altered exposure to phenytoin suggests that monitoring of phenytoin plasma concentrations may be warranted.

The results in this abstract have been previously presented in part at the American Academy of Neurology Annual Meeting, April 2011, Honolulu, Hawaii using Phase 3 data from 2 studies.