Analysis of changes in plasma sodium levels and related treatment-emergent adverse events during short- and long-term use of eslicarbazepine acetate as adjunctive and monotherapy

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OBJECTIVE

To examine the effects of ESL on plasma sodium levels and the incidence of hyponatremia-related treatment-emergent adverse events (TEAEs) in a post-hoc analysis of data from Phase III clinical trials of ESL.

INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily olanzapine 2-methyltetrahydroisoquinoline (mTHIQ) drug for the treatment of partial-onset seizures (POS).
- ESL is a member of the dibenzazepinedicarboxamide class of putative voltage-gated sodium channel blockers, which also includes carbamazepine (CBZ) and oxcarbazepine (OXC).
- Development of hyponatremia has been associated with the use of dibenzazepine carboxamide AEDs.
- Therefore, it is of value to investigate the frequency of hyponatremia in controlled and uncontrolled Phase III clinical trials of ESL.

METHODS

Study design

- Data from the three Phase III studies (and four open-label extensions (OLEs)) were analyzed:
  
  - Adjunctive ESL
  
  - Three randomized, double-blind, placebo-controlled trials: BA-200-301 (NCT00667207), -302 (NCT00750714) and -304 (NCT00988429).4
  
  - ESL monotherapy:
  
  - Two randomized, dose-blind, conversion-to-monotherapy studies with a historical control comparator: 5 500-MLC (NCT00866775) and 500-MLC (NCT00910619).4
  
  - OLEs of studies 041 and 043: 093-010 (NCT01216124),4
  
- Inclusion criteria:

  - ≥16 years (≥18 years for studies 301 and 302)
  
  - Refractory POS (i.e., patients who had failed ≥2 treatments or ≥3 ≥125 mEq/L, and proportion of patients with >10 mEq/L decrease in sodium levels (≤125 mEq/L) were reported for 11 (1.1%) patients in the controlled trials of ESL monotherapy.

Sodium levels

- Changes from baseline in plasma sodium levels, proportion of patients with clinically meaningful minimum post-dose sodium levels (≤125 mEq/L), and proportion of patients with ≥10 mEq/L decrease in sodium levels (≤125 mEq/L) were reported for 11 (1.1%) patients in the controlled trials of ESL monotherapy.

- After an 8-week baseline period, patients taking 1–2 AEDs were randomized to receive placebo or ESLs 400 mg (studies 301 and 302), 800 mg or 1200 mg QD; the 14-week double-blind period comprised:

  - Adjunctive ESL
  
  - Two randomized, dose-blind, conversion-to-monotherapy studies with a historical control comparator: 5 500-MLC (NCT00866775) and 500-MLC (NCT00910619).4
  
  - OLEs of studies 041 and 043: 093-010 (NCT01216124),4

- Inclusion criteria:

  - Age ≥16 years (≥18 years for studies 301 and 302)
  
  - Refractory POS (i.e., patients who had failed ≥2 treatments or ≥3 ≥125 mEq/L) according to clinical laboratory analyses.

- Changes from baseline in plasma sodium levels, proportion of patients with clinically meaningful minimum post-dose sodium levels (≤125 mEq/L), and proportion of patients with ≥10 mEq/L decrease in sodium levels (≤125 mEq/L) were reported for 11 (1.1%) patients in the controlled trials of ESL monotherapy.

- Monitoring of plasma sodium levels should be considered during ESL treatment, particularly for patients with a history of hyponatremia, or conditions that may increase the risk of hyponatremia, such as infection, inflammation, fluid overload, seizures, headache, or dehydration.

Studying the relationship between sodium levels and TEAEs has been previously reported for patients taking ESL as monotherapy.

CONCLUSIONS

- Reductions in plasma sodium levels and related TEAEs were reported for some patients taking ESL.

- Monitoring of plasma sodium levels should be considered during ESL treatment, particularly for patients with a history of hyponatremia, or conditions that may increase the risk of hyponatremia, such as infection, inflammation, fluid overload, seizures, headache, or dehydration.

REFERENCES


DISCLOSURES

Robert T Wechsler, 1 Rodney A Radtke, 2 Kenneth D Laxer, 3 Eugen Trinka, 4 Marianna Vieira, 4 Joana Moreira, 4 Francisco Rocha, 4 Hailong Cheng, 4 Todd Grinnell, 4 David Blum 5

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