Eslicarbazepine acetate monotherapy: a population pharmacokinetic analysis

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Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED), approved by the US Food and Drug Administration for the treatment of partial-onset seizures (POS) as monotherapy or adjunctive therapy. ESL is approved by the European Medicines Agency as adjunctive therapy of POS in adults.

ESL is rapidly and extensively metabolized to eslicarbazepine,4 which is thought to act primarily by preferentially stabilizing the neuronal state of voltage-gated sodium channels.5

The efficacy and safety of ESL monotherapy (1320 mg and 1600 mg QD) have been explored in two Phase III studies in patients with POS, which demonstrated superior efficacy to a historical control and a safety/tolerability profile consistent with that reported for adjunctive ESL.2,6

We here report the development of a population pharmacokinetic (PK) model for eslicarbazepine during ESL monotherapy.

OBJECTIVE

To develop a population PK model and to characterize the disposition of eslicarbazepine during once-daily ESL monotherapy in adults.

METHODS

Study designs and populations

Phase I studies

• The design of the two Phase II conversion-to-monotherapy studies (939-045 and -048) has been reported previously.4

• Population: Patients were aged 16–70 years with POS (with or without secondary generalization) not adequately controlled by one to two AEDs. Inclusion criteria included:
  – ≥ 24 POS in the 9 weeks prior to screening
  – maximum of one concomitant sodium channel blocker
  – elderly patients (age 65–70 years) must have had no additional health concerns.

• Titration period (Weeks 1–3)

  While maintaining stable doses of concomitant AEDs, ESL was initiated and titrated over 3 weeks to 1200 mg QD (Week 1: 400 mg QD; Week 2: 800 mg QD; Week 3: 1200 mg QD).

• Conversion-to-monotherapy period (Weeks 3–9)

  Doses of concomitant baseline AEDs were tapered off.

• Monotherapy period (10 weeks): Patients continued to receive the target dose of ESL as monotherapy.

Phase II studies

• Data from 10 Phase I studies of ESL monotherapy (with conditions that matched those of the Phase II clinical trials) were included in the analyses: 2093-013, -014, -015, -109, -110, -113, -115, -116, -121, -120, -121, -127, and -129.

• Multiple-dose studies in healthy volunteers (male and female): ESL 600, 800, 900, and 1200 mg QD, with collection of plasma samples during the 24-hour internal following dosing.

Measurement of eslicarbazepine in plasma samples

• Plasma samples were collected and eslicarbazepine concentrations determined by validated chiral liquid chromatography with tandem mass spectrometry. The lower limit of quantitation for eslicarbazepine was 0.05 µg/mL.

• In Phase II studies, during the ESL monotherapy period, 1–2 plasma samples were collected per patient (at most patients), in the 24-hour period after each dose.

• In Phase I studies, 12–21 plasma samples were collected per subject during the 24-hour period after each dose.

Experatory data analysis

• Exploratory analyses and visualizations were used to understand the dataset, search for outliers, assess possible trends and relationships, model formulation, and identify any errors in dataset construction or manipulation.

Pharmacokinetic modeling

• The dataset comprised eslicarbazepine plasma concentrations from all 12 studies (10 Phase I and 2 Phase II studies).

• A previously developed population PK structural model for eslicarbazepine was applied for the dataset and the further refined.

• An exploratory dataset was used to explore the inter-individual variability (IN) in:
  – absorption rate constant (ka)
  – apparent oral clearance (CL/F, CL: clearance; F: bioavailability)
  – apparent volume of distribution (V/F)

• Two separate, additive plus constant, coefficient of variation error models were used to describe residual error.

• Statistically significant predictors of PK variability were identified using a univariate forward–backward elimination method, assessing a number of covariates:
  – age, weight, body mass index (BMI), race, gender, and creatinine clearance (CrCl).

• Concordance between simulated data using the final model and observed data was validated using a visual predictive check.

RESULTS

Dataset

• In total, 4629 estimates of plasma eslicarbazepine concentration from 569 individuals were evaluated.

• After exclusions, 3869 estimates from 493 individuals were analyzed.

• Concomitant carbamazepine was taken by 36% of subjects, and phenytoin by 10% of subjects in the Phase II monotherapy trials PK population. Other inducing AEDs (barbiturates) were excluded from analysis.

Exploratory data analysis

• Concentration-time profiles for the pooled dataset showed linear kinetics within the dose range explored.

• Dose-normalized eslicarbazepine concentrations overlapped between subjects in the Phase I and Phase II studies.

• During the monotherapy phase, variability between patients in plasma eslicarbazepine concentrations (and the changes in concentration over time) was similar for subjects who had taken carbamazepine, phenytoin, and other AEDs during the baseline period.

• Thus, effects of other AEDs on eslicarbazepine PK (mediated via effects on cytochrome P450 enzymes) were not evident during the monotherapy phase.

Model-predicted population pharmacokinetic parameters

• The final population PK model was a one-compartment model with first-order absorption and first-order elimination.

• The population PK parameters predicted by the final model (plus the related estimates of precision [95% CI]) are shown in Table 1.

• The estimated first-order absorption half-life was 0.654 hours.

• The estimated elimination half-life in subjects of median body weight was approximately 16 hours in females and 17 hours in males.

Table 1. Population model-PK parameter estimates for the final model of eslicarbazepine acetate PK monotherapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final population mean (95% CI)</th>
<th>Male (N=249)</th>
<th>Female (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN ka</td>
<td>1.06 (0.74–1.52)</td>
<td>1.13 (0.74–1.59)</td>
<td>1.00 (0.70–1.45)</td>
</tr>
<tr>
<td>CL/F</td>
<td>2.31 (0.31–14.8)</td>
<td>2.26 (0.31–14.8)</td>
<td>2.36 (0.31–14.8)</td>
</tr>
<tr>
<td>Additive shift in CL/F for female gender</td>
<td>-0.40 (0.31–14.8)</td>
<td>-0.53 (0.31–14.8)</td>
<td></td>
</tr>
<tr>
<td>IN V/F</td>
<td>62.0 (30.3–14.8)</td>
<td>63.2 (30.3–14.8)</td>
<td>60.5 (30.3–14.8)</td>
</tr>
<tr>
<td>Additive shift in V/F for female gender</td>
<td>-0.76 (0.31–14.8)</td>
<td>-0.76 (0.31–14.8)</td>
<td></td>
</tr>
</tbody>
</table>

The predicted variability in CL/F and V/F with body weight and gender showed minimal differences. The variability in elimination half-life is predicted to result in, at most, a difference of 2 days in time to steady state, between the lowest and highest weight percentiles.

Table 2. Predicted impact of body weight on eslicarbazepine exposure (AUC0–24h) during ESL monotherapy

<table>
<thead>
<tr>
<th>Body weight percentile</th>
<th>Male (N=249)</th>
<th>Female (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st percentile (48 kg)</td>
<td>13.6% higher</td>
<td>15.2% higher</td>
</tr>
<tr>
<td>50th percentile (74 kg)</td>
<td>13.6% lower</td>
<td>15.2% lower</td>
</tr>
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• The estimated V/F was 62.0 L at the median body weight of 74.4 kg, eslicarbazepine V/F is predicted to be 59.4 L/kg for a male subject and 64.7 L/kg for a female subject, while eslicarbazepine CL/F is predicted to be 2.6 L/hr (0.03 L/hr/kg) for a male subject and 2.32 L/hr (0.03 L/hr/kg) for a female subject.

• These parameters are consistent with the results of a population PK analysis for eslicarbazepine acetate in POS patients (2093-011, -021, -024) and ESL in 61.3 L in subjects not using adjunctive therapy using a one-compartment PK model (1096-002).

• The inter-individual variability was high for k0 and moderate for CL/F and V/F.

• The residual variability of the Phase II model was moderate (30.2% coefficient of variation (CV)) while the residual variability of the Phase I data was higher at the lower concentration (25.5% CV for 3.5 µg/mL) than at the higher concentration (11.7% CV for 39.5 µg/mL).

Predictors of pharmacokinetic variability, and effects on pharmacokinetic parameters

• Body weight and gender were found to be statistically significant predictors of both CL/F and V/F.

• Neither age nor race had a statistically significant effect on CL/F or V/F.

• Although the effects of body weight and gender on CL/F and V/F were statistically significant, the consequential impact on exposure was not clinically relevant.

• Neither age nor race had a significant effect on eslicarbazepine PK parameters.

• The effects of body weight and gender on CL/F and V/F were statistically significant, the consequential impact on exposure was not clinically relevant.

• Consequently, during ESL monotherapy, no dose adjustments are required to account for differences in body weight and gender.

CONCLUSIONS

• During ESL monotherapy, plasma eslicarbazepine concentrations were described by a one-compartment model with first-order absorption and linear elimination.

• The doses of ESL used in the monotherapy trials (1320 mg and 1600 mg QD) were higher than the therapeutic dose of ESL taken by 29% of subjects during ESL monotherapy trials.

• Although the effects of body weight and gender on CL/F and V/F were statistically significant, the consequential impact on exposure was not clinically relevant.

• Thus, effects of other AEDs on eslicarbazepine PK (mediated via effects on cytochrome P450 enzymes) were not evident during the monotherapy phase.

REFERENCE

1. P1.15

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