CNS Drugs

Pharmacokinetics, Drug Interactions and Exposure-Response Relationship of Eslicarbazepine Acetate in Adult Patients with Partial-Onset Seizures

Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

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Supplemental Digital Content

This Supplemental Digital Content contains the modelling methods referred to in the full version of this article, which can be found at http://adisonline.com/cnsdrugs

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Population pharmacokinetics, drug interactions and exposure-response relationship of eslicarbazepine acetate (ESL) in adult patients with partial-onset seizures

GENERAL CONSIDERATIONS FOR DATA ANALYSES

Method for pharmacokinetics (PK) and statistical model building

NONMEM (version V, level 1.1, Regents of the University of California, San Francisco, USA) was used in this analysis. NONMEM is a suite of programs including a data and code pre-processor (NM-TRAN) and a library of PK subroutines (PREDPP), which offers a vast array of PK modules able to predict concentrations of drugs in plasma or other PK compartments. If one wants to write user-defined PK models or if information in the data is not sufficient to estimate all parameters needed by a PREDPP PK model, then one may use NM-TRAN to write a prediction subroutine (PRED) to fit a user model to the data.

EMF Consulting constructed the NONMEM datasets. Data assembly and coding for population PK analysis with NONMEM used the specifications described in the pre-defined data analysis plan.

The population PK analysis is based on multiple regression using non-linear mixed effect models. Mixed effect models describe the influence of both fixed effects and random effects on a dependent variable, e.g. plasma drug concentration or a clinical endpoint. Fixed effects, THETA (θ) in NONMEM notation, are factors that are either measured or controlled. Random effects include residual error (ERR), epsilon (ε) in NONMEM notation, and between subject random effects, ETA (η) in NONMEM notation.

The population PK mixed effects models include traditionally four basic components:
- The structural PK model, which predicts the plasma concentration as a function of time and dose.
- The covariate model component, which describes the influence of fixed effects (demography, disease, concomitant medications) on PK model population parameters.
- The between-subject variance component, which describes the inter-individual variation in PK parameters (after “correction” for fixed effects).
- The residual error model components, which describes the underlying distribution of the error in the measured PK variable.

In our analyses we followed this approach. The structural model was built first, including error models. Then covariates were added as necessary, using a predefined strategy. The final model should have no redundant factor but the strategy should ensure that no significant factor was missed. The following steps were followed:

1. Selection of the simplest structural model, to use as a valid base model, based on smallest objective function and by inspection of the pattern in the residual plots. The best estimation method, the most appropriate between-subjects variance models, and the residual error model, were identified. The resulting model was called a BASE model.

2. Selection of covariates by univariate analyses, at risk 0.01 (reduction of objective function of at least 6.63). The best model for each covariate to affect each of the parameters was selected at this stage.

3. Multivariate analysis: all selected covariates were added together and the model fitted to data. This reference was called FULL model.

4. Backward deletion was applied until no covariate could be removed without significantly increasing the objective function, resulting in the FINAL model (likelihood ratio test at p<0.001, 1 df, objective function drop of at least 10.83).

5. If a confidence interval (CI) of structural parameters included the value zero, the effect was considered not significant and the model was further simplified until all structural parameters were well estimated.
Model acceptability and estimation method

Acceptable population models were to result in successful minimization, with at least three significant digits for any parameter, a successful estimation of the covariance, and the absolute value of last iteration gradients greater than $10^3$ but smaller than 100. Confidence intervals of structural parameters should not include zero; absolute value of correlation between two structural parameters should not be greater than 0.95.

Acceptable models should not lead to trends in the distribution of weighted residuals versus model predictions and versus independent variable. They should not be over-sensitive to initial estimates. The observations versus predictions data should be evenly distributed around the unit line, as evidenced by series of diagnostic plots. If constraints were applied on parameters, no final estimate should be equal to its boundary. Since the data set consisted exclusively of sparse data, the first order (FO) or the first order conditional estimation method (FOCE) may perform equally well.

Derived variables

Age (AGE, years) was derived as: \( \text{AGE} = (\text{date of assessment} - \text{date of birth}) / 365.25 \).

Creatinine clearance (\( CL_{CR} \), mL/min) was estimated from serum creatinine according to the Cockcroft and Gault equation:

\[
CL_{CR} \text{ (mL/min)} = \frac{140 - \text{AGE} \times WT(kg) \times k}{72 \times S_{CR} \text{ (mg/dL)}},
\]

where \( k=1 \) for males and \( k=0.85 \) for females.

Study Population

Summary statistics of the PK population were produced, including tables with demographic variables, laboratory safety covariates and AED concomitant populations. Patients enrolled in the studies who did not provide any valid PK assessment during treatment were excluded from the description of the PK population.

PHARMACOKINETIC ANALYSES

PREDPP PK structural model

The model initially assessed on the pool of data from the double-blind phases of the studies was a one-compartment PK model with FO absorption and elimination, the absorption rate constant describing the rate of appearance of eslicarbazepine in plasma rather than its rate of absorption since ESL is the prodrug. However, the structure of the data showed that only a few samples appeared to have been collected during the first hours post-dose, limiting the information available to estimate the volume of distribution and the rate constant of absorption. Moreover, there was no trending for a decrease of concentrations over the 24-hour period following the administration, which infirm the assumption that the treatment doses were taken exactly according to the protocol.

PRED PK user-defined structural model

Since only one sample post-dose was available from each subject, most of them being pre-dose samples, a simple population PK screen had to be used, i.e. the model estimated only one parameter, the apparent clearance (\( CL/F \)), which is sufficient to predict average concentrations at steady-state (\( C_{av-steady} \)).

Since the interval between two doses was 24 hours, and prior PK data collected in
healthy subjects have shown that the elimination half-life (t_{1/2}) determined by non-compartmental analysis was approximately 10 hours, the pre-dose concentration at steady-state (C_{\text{min-ss}}) cannot be approximated by C_{\text{av-ss}}. Instead, prior information was needed to derive C_{\text{min-ss}} from CL/F and a rate constant of elimination (K_e), using the equation:

\[ C_{\text{min-ss}} = \frac{\text{Dose} \cdot F \cdot e^{t \cdot K_e}}{\text{CL} / K_e \cdot \left(1 - e^{-t / K_e}\right)} \]

where \( \tau \) is the dosing interval.

K_e could be derived from clearance and V, if V was known and could be fixed to a given value for all subjects, or K_e could be derived from t_{1/2}, also to be fixed to the same value for all subjects.

Allometric scaling was used as a prior in the base model and its statistical significance was not tested: clearance is defined as a function of body weight centred on a typical value with exponent 3/4.

**Statistical models selection**

A proportional error, a constant additive error, and a combination of both error models were evaluated for the residual error of the PK and of the PRED model:

- Additive error model: \( Y_{ij} = F_{ij} + \epsilon_{ij1} \)
- Proportional error model: \( Y_{ij} = F_{ij} \cdot (1 + \epsilon_{ij1}) \)
- Combined error model: \( Y_{ij} = F_{ij} \cdot (1 + \epsilon_{ij1}) + \epsilon_{ij2} \)

where \( Y_{ij} \) is the \( i^{th} \) value observed in the \( j^{th} \) individual, or its log transform, \( F_{ij} \) is the predicted value of the PK model, \( \epsilon_{ij1} \) and \( \epsilon_{ij2} \) are the random errors with zero mean and variance \( \Sigma \) to be estimated.

With the PREDP one-compartment model as for the PRED model, between-subject random effects were explored on clearance only. An exponential model was preferred:

\[ P_j = \text{TVP} \cdot \exp(\eta_j) \]

where \( P_j \) TVP is the individual PK parameter (CL) for the \( j^{th} \) individual, TVP is the typical value of the population parameter, and \( \eta_j \) is the between-subject random effect with zero mean and variance \( \Omega \) to be \( \eta_j \) estimated.

The joint distribution of \( \eta_j \) and \( \epsilon_{ij} \) is assumed normal with mean 0 and variance-covariance matrices omega (\( \Omega \)) for \( \eta_j \) and sigma (\( \Sigma \)) for \( \epsilon_{ij} \) to be estimated.

**Covariate analysis**

The effect of the following covariates on CL/F of eslicarbazepine was investigated:

i. The effect of ESL dose.

ii. Demographic data (height, age, and sex) were explored; functions of height (centred on its median) were to be explored first, and then saturable models could be explored as needed.

iii. The relationship of PK with kidney function, using estimates of CLCR.

iv. The relationship of PK with liver function using the hepatic laboratory values: aspartate aminotransferase (ASAT), alanine transaminase (ALAT), and gamma-glutamyltransferase (GGT).

v. Since ESL is administered for a long period of time, the effect of time in the study on clearance was investigated.

vi. The effect of concomitant AEDs; only AEDs administered simultaneously with ESL to 15% of the subjects or at least to 20 subjects were considered for the analysis of PK drug-drug interactions.

The effect of concomitant AEDs was analysed sequentially, by: presence/ absence, effect of doses and/or effect of concentrations. The AEDs considered were: lamotrigine, valproate, gabapentin, phenytoin, carbamazepine, topiramate, phenobarbital, clobazam and
levetiracetam.

The list of covariate models tested, depending on the nature of the covariate (continuous or categorical, physiological marker or related to study procedure), is presented in Table 1.

Table 1. List of covariate models

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Model tested</th>
</tr>
</thead>
</table>
| Height, age, other continuous covariates | \[ TVP = P_{POP} + \theta_1 \times (\text{COV}_i - \text{Median}_{\text{COV}_i}) \]  
\[ TVP = P_{POP} \times \left( \frac{\text{COV}_i}{\text{Median}_{\text{COV}_i}} \right)^{\text{III}} \] |
| Dose or concentration of AEDs           | \[ TVP = P_{POP} + \theta_1 \times \text{COV}_i \]  
\[ TVP = P_{POP} + \frac{\theta_1 \times \text{COV}_i}{\theta_2 + \text{COV}_i} \] |
| Time in the study in days (NDAY)        | \[ TVP = P_{POP} + \theta_1 \times \text{COV}_i \] |
| Categories: sex, race, presence of AED, regimen, study effects etc | \[ TVP = P_{POP} + \theta_1 \times \text{COV}_i \] |

1. TVP is the parameter for the "typical" individual with covariate value COV,
2. PPOP is the population parameter for the PK parameter P,
3. COVI is the individual value for the covariate (e.g. body size),
4. III is a population parameter to estimate.

Model qualification

Diagnostic plots were provided over the entire dataset, including plots of population and individual prediction versus observations, of weighted residuals versus population predictions and versus time after dosing.

The population PK model was qualified using performance predictive checks. Depending on the actual number of subjects, an appropriate number of Monte Carlo simulations (replications) were performed using the final model with NONMEM.

Visual and numerical predictive checks were performed using SAS (SAS Institute, Cary, NC): percentiles of the observed data were superimposed with the percentiles derived from the simulated data and compared visually. Summary statistics of observed and simulated data with Mean Square Error (MSE) and Root Mean Square Error (RMSE) were provided. Percentiles were represented as figures using SigmaPlot (Systat Software Inc, Chicago, IL).

Exposure parameters

The PK parameters were calculated using NONMEM and exposure parameters, C_{min-ss}, C_{2\text{V}-\text{ss}} and AUC_{24-\text{ss}}, were derived. The exposure parameters for a one compartmental model with FO elimination were calculated as follows:

\[
\text{AUC}_{24-\text{ss}} = \frac{\text{Total Daily Dose}}{\text{CL} / F}
\]

\[
C_{\text{min-ss}} = \frac{\text{Dose}}{\text{CL} / F / K_e} \cdot \frac{e^{(-K_e \cdot t)}}{1 - e^{(-K_e \cdot t)}}
\]

\[
C_{\text{ss-ss}} = \frac{\text{AUC}_{24-\text{ss}}}{24}
\]
where $\tau$ is the dosing interval, $V/F$ is the apparent volume of central compartment, $CL/F$ is the apparent clearance, and $Ke$ is the elimination rate constant, obtained dividing the clearance by the volume.

**Drug concentration data**

The PREDPP NONMEM dataset comprised records from 1048 different individuals treated with either ESL or placebo, during the maintenance, double-blind phase of the studies. The population PK modelling analysis was performed on a population of 641 subjects who had been treated with ESL and presented valid PK information.

Scatter plots of concentrations versus the time relative to dosing in the PREDPP dataset are presented in Figure 1 to Figure 4.

![Figure 1](image1.png)

**Figure 1. Plot of concentrations of eslicarbazepine (BIA 2-194) versus time relative to dosing at the end of 12 weeks of treatment (Visit 5)**
Figure 2. Plot of concentrations of eslicarbazepine (BIA 2-194) versus time relative to dosing at the end of the 12 weeks of treatment (Visit 5) with ESL 400 mg
Figure 3. Plot of concentrations of eslicarbazepine (BIA 2-194) versus time relative to dosing at the end of 12 weeks of treatment (Visit 5) with ESL 800 mg
Figure 4. Plot of concentrations of eslicarbazepine (BIA 2-194) versus time relative to dosing at the end of 12 weeks of treatment (Visit 5) with ESL 1200 mg

The plots of concentrations versus time relative to dosing do not display any trend to a decrease, which would be needed to estimate the PK parameters describing the elimination of ESL, the rate constant of elimination.

**Base model using a one-compartment PREDPP**

A one-compartment model (ADVAN1) without any absorption parameter was used, with only two PK parameters (CL/F and volume of distribution, Vd), one random effect to describe between subjects’ variability on those parameters, and a series of different models
for the residual error. Observed and predicted concentrations (population and individual) versus time relative to dosing, from a one-compartment model, are presented in Figures 5 and 6.

**Figure 5.** Observed and predicted population concentrations of eslicarbazepine (BIA 2-194) from a one-compartment PREDPP model
Figure 6. Observed and predicted individual concentrations of eslicarbazepine (BIA 2-194) from a one-compartment PREDPP model

The estimated structural parameters were very different from those derived by non-compartmental analysis of rich PK profiles collected during Phase I studies. With an additive residual error, CL/F was estimated at 6.49 L/h; Vd was estimated at ~3900 L with large residual error and large between-subjects variability.

An important number of attempts at modelling the concentration-time data failed. They demonstrated an important “shrinkage” of the between subjects differences (etas), which may prevent proper estimation of parameters. The structure of the data themselves, with only one trough sample per subject, prevented the separation of the random effects in between and within subjects’ variability. Therefore, most analyses used a user-model (PRED) for $C_{\text{min-ss}}$ using the regimen prescribed during the 12-week maintenance period.
Base model using a user-defined PRED

Initially, a number of models were estimated using the observations on their actual scale. However, the predictions were often over-predicted in the lower range of concentrations. The data were thus transformed and the latest models fitted the log(DV) rather than the actual data, resulting in comparable parameter estimates and less bias in predictions at low concentrations.

The assumption was made that the $C_{\text{min}-\text{ss}}$ after oral administration is similar to that after intravenous dosing, which is a reasonable assumption since the $t_{\text{max}}$ in phase I rich PK studies with ESL is short, relative to the 24-hour dosing interval. The terminal elimination $t_{1/2}$ was approximately 10 h, resulting in $K_e = 0.693/10 = 0.0693$ h$^{-1}$. Using the $C_{\text{min}-\text{ss}}$ equation, the estimation produced clearance estimates in line with those obtained by non-compartmental analysis of healthy subjects’ data and less bias in the predicted concentrations.

Clearance was affected by body weight using the allometric equation with power 3/4. The between subject variability was estimated using an exponential function. The residual error was proportional to the logarithm of the predicted concentration.

The population estimates for the base model are reported in Table 2 and goodness-of-fit plots are presented in Figure 7.

Table 2. **Population PK parameters – Base model, user-defined PRED model**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate</th>
<th>SEE</th>
<th>95% CI</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL/F$ (L/h) = $(\theta_1 + \theta_2<em>DOST)</em>\text{(Weight/70)}$ <strong>0.75</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta_1$</td>
<td>Intercept $CL/F$ (L/h)</td>
<td>3.36</td>
<td>0.159</td>
<td>[3.05; 3.67]</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>Effect of ESL dose (L/h)</td>
<td>-0.217</td>
<td>0.159</td>
<td>[-0.529; 0.095]</td>
</tr>
<tr>
<td><strong>Random Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Inter individual variance (exponential)}$</td>
<td>$\text{ILV on } CL/F$</td>
<td>0.263</td>
<td>0.0259</td>
<td>[0.212; 0.314]</td>
</tr>
<tr>
<td>$\text{Residual variability on log (conc)}$</td>
<td>$\sigma^2$ proportional</td>
<td>0.00364</td>
<td>0.00028</td>
<td>[0.00309; 0.00419]</td>
</tr>
</tbody>
</table>

*DOST=1 if ESL dose > 400 mg, DOST=0 otherwise
Figure 7. Goodness of fits plots – base model using a PRED user-defined model

The population value for eslicarbazepine CL/F was 3.36 L/h for a subject taking a daily dose of ESL 400 mg and 3.14 L/h for a subject taking a daily dose of ESL greater than 400 mg. The between subjects’ variability on CL/F was 51% and the residual error had a CV 6% in log scale.

Final user-defined PRED model

Some covariates did not affect significantly the CL/F of eslicarbazepine and were not evaluated further: gender, age, race (Non-Caucasian vs. Caucasian), CL_CR, alkaline phosphatise (ALP), ALAT, ASAT and bilirubin; effect of lamotrigine, topiramate, and levetiracetam.
Liver function as bilirubin, valproate concentrations, barbiturates (presence/absence), and carbamazepine daily dose were included into a full model. Backward deletion was applied. The resulting model included only the carbamazepine daily dose and the presence/absence of “barbiturates”, i.e. phenobarbital-like inducers. Since barbiturates and carbamazepine are both inducers, a potential interaction between barbiturates and carbamazepine was evaluated; the magnitude of the interaction factor between these AEDs was not significant.

Since the effect of dose of ESL on clearance was estimated with low precision, it was subsequently removed from the model. When only the effects of carbamazepine dose and the presence/absence of barbiturate-like inducers were retained, the minimization was successful and the variance-covariance matrix was obtained. All parameters were precisely estimated with 95% CI not including zero. The population estimates for the final model are reported in Table II and diagnostic plots are presented in Figure 1 of the manuscript.

### Sensitivity analysis

A sensitivity analysis was done to consolidate the assumption that the prediction of $C_{\text{min-s}}$ may use $K_e$ derived from $t_{1/2}$ instead of deriving $K_e$ from $CL/F$ and $V_d$. The final model was used to assess the sensitivity of the analysis to the assumption that $t_{1/2}$ was 10 hours.

The model was evaluated initially by varying $t_{1/2}$ between 7 h to 14 h. Various estimates of $CL/F$ were obtained and compared with the reference ($t_{1/2} = 10$ h, $CL/F = 2.36$ L/h). Table 3 presents the results of this analysis.

<table>
<thead>
<tr>
<th>Half-life (h)</th>
<th>Estimated CL (L/h)</th>
<th>NONMEM Objective function</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1.48</td>
<td>67.589</td>
</tr>
<tr>
<td>8</td>
<td>1.81</td>
<td>67.589</td>
</tr>
<tr>
<td>9</td>
<td>2.10</td>
<td>67.590</td>
</tr>
<tr>
<td>11</td>
<td>2.60</td>
<td>67.590</td>
</tr>
<tr>
<td>12</td>
<td>2.81</td>
<td>67.590</td>
</tr>
<tr>
<td>13</td>
<td>3.00</td>
<td>67.589</td>
</tr>
<tr>
<td>14</td>
<td>3.16</td>
<td>67.590</td>
</tr>
</tbody>
</table>

The same method was used to derive $K_e$ and assess $CL/F$ while varying $V_d$ with the following values, 26, 28, 30, 32, 34, 36 and 38 L; results are shown in Table 4.

When $t_{1/2}$ was fixed from 7 to 14 hours, the $CL/F$ estimate varied by a factor 2.14 while the objective function did not change at all, suggesting that the data carry no information about $V_d$. On the opposite, when $V_d$ was fixed to a hypothetical value, varying by a factor 2, $CL/F$ estimates varied by a factor 1.41 and were associated with larger changes of the objective function. Moreover, the minimization was more sensitive to initial estimates than with a fixed $t_{1/2}$. No run with values lower or larger than the $V_d$ limits used here were successful. In both cases, the effects of carbamazepine co-administration were very stable and estimated at the same value. It was therefore concluded that the initial assumption that $C_{\text{min-s}}$ could be predicted under the assumption that $t_{1/2}$ was close to 10 hours was acceptable.
Table 4. Sensitivity analysis with varying value of Vd

<table>
<thead>
<tr>
<th>V/F (L)</th>
<th>Estimated CL (L/h)</th>
<th>NONMEM Objective function</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>2.07</td>
<td>239.521</td>
</tr>
<tr>
<td>28</td>
<td>2.15</td>
<td>231.581</td>
</tr>
<tr>
<td>30</td>
<td>2.23</td>
<td>224.392</td>
</tr>
<tr>
<td>32</td>
<td>2.31</td>
<td>217.846</td>
</tr>
<tr>
<td>34</td>
<td>2.38</td>
<td>211.855</td>
</tr>
<tr>
<td>36</td>
<td>2.45</td>
<td>206.348</td>
</tr>
<tr>
<td>38</td>
<td>2.52</td>
<td>201.266</td>
</tr>
<tr>
<td>42</td>
<td>2.65</td>
<td>192.185</td>
</tr>
<tr>
<td>48</td>
<td>2.82</td>
<td>180.730</td>
</tr>
<tr>
<td>52</td>
<td>2.92</td>
<td>174.225</td>
</tr>
</tbody>
</table>

PK model qualification

Performance predictive checks were performed using 500 replications of the analysis dataset and the model estimated, and their results are summarised by percentiles and measures of prediction error in Table 5.

Table 5. Summary of simulated concentrations (performance predictive checks) by dose

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Obs mean</th>
<th>Sim mean</th>
<th>Obs geomean</th>
<th>Sim geomean</th>
<th>MPE</th>
<th>ME</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 103999</td>
<td>2470.6</td>
<td>3011.4</td>
<td>1888.9</td>
<td>2324.0</td>
<td>540.8</td>
<td>2075.9</td>
<td>3149.5</td>
</tr>
<tr>
<td>800 354000</td>
<td>5391.5</td>
<td>6411.0</td>
<td>4188.7</td>
<td>4815.1</td>
<td>1019.5</td>
<td>4418.1</td>
<td>7012.1</td>
</tr>
<tr>
<td>1200 161500</td>
<td>8523.1</td>
<td>9605.0</td>
<td>6749.8</td>
<td>7136.3</td>
<td>1082.0</td>
<td>6756.6</td>
<td>10404.0</td>
</tr>
</tbody>
</table>

The comparison of percentiles of observed and simulated data show adequate performances of the model by study and dose of ESL, although low concentrations are less well predicted which can be explained by possible lack of compliance.

Overall, the model estimated as the final model is an acceptable model and represents the data appropriately.

Eslicarbazepine-derived exposure PK parameters

A summary of individual estimates of eslicarbazepine CL/F and of derived exposure parameters AUC_{24-ss} and C_{av-ss} by dose is presented in Table 6.
Table 6. Summary of individual PK parameters by dose

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>N</th>
<th>Geometric Mean</th>
<th>90% CI</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>158</td>
<td>3.40</td>
<td>3.20 ; 3.60</td>
<td>3.55</td>
<td>1.09</td>
<td>8.29</td>
</tr>
<tr>
<td>800</td>
<td>295</td>
<td>3.20</td>
<td>3.00 ; 3.20</td>
<td>3.04</td>
<td>0.97</td>
<td>12.69</td>
</tr>
<tr>
<td>1200</td>
<td>188</td>
<td>3.00</td>
<td>2.80 ; 3.20</td>
<td>3.01</td>
<td>0.83</td>
<td>8.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>N</th>
<th>Geometric Mean</th>
<th>90% CI</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>158</td>
<td>4972.7</td>
<td>4677.3 ; 5286.9</td>
<td>4690.7</td>
<td>2010.7</td>
<td>15247.2</td>
</tr>
<tr>
<td>800</td>
<td>295</td>
<td>10631.1</td>
<td>10195.5 ; 11085.4</td>
<td>10967.1</td>
<td>2627.8</td>
<td>34308.7</td>
</tr>
<tr>
<td>1200</td>
<td>188</td>
<td>16513.6</td>
<td>15764.4 ; 17298.5</td>
<td>16595.1</td>
<td>6190.0</td>
<td>59891.0</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Daily dose</th>
<th>N</th>
<th>Geometric Mean</th>
<th>90% CI</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>158</td>
<td>119346.0</td>
<td>112254 ; 126886</td>
<td>112576.7</td>
<td>48257.3</td>
<td>385931.8</td>
</tr>
<tr>
<td>800</td>
<td>295</td>
<td>255146.8</td>
<td>244692 ; 266049</td>
<td>263209.8</td>
<td>63066.6</td>
<td>823409.5</td>
</tr>
<tr>
<td>1200</td>
<td>188</td>
<td>396326.7</td>
<td>378345 ; 415163</td>
<td>398282.5</td>
<td>148559.0</td>
<td>1437384</td>
</tr>
</tbody>
</table>

CL/F (geometric mean) in the pooled population ranged between 3.0 and 3.4 L/h, which is expected since more than 50% of patients received concomitantly carbamazepine, and 13% of patients received barbiturate-like inducers.

Overall, the predicted $C_{avss}$ (geometric mean) is 4,972.7 ng/mL for 400 mg, 10,631.1 ng/mL for 800 mg and 16,513.6 ng/mL for 1200 mg. Similarly, the predicted AUC$_{24ss}$ (geometric mean) values were 119,346.0 ng/mL.h, 255,146.8 ng/mL.h and 396,326.7 ng/mL.h for ESL 400 mg, 800 mg and 1200 mg respectively.