Population Pharmacokinetics of Brivaracetam in Patients With Partial Epilepsy

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RATIONAL

- Brivaracetam (BRV) is a novel SV2A ligand currently under Phase III development for epilepsy.
- BRV has a 10-fold higher affinity for SV2A than levetiracetam and also has inhibitory activity at neuronal voltage-dependent sodium channels.
- BRV is completely absorbed, is weakly bound to plasma proteins, has a plasma half-life of approximately 8 hours, is extensively metabolized through several non-CYP- and CYP-dependent pathways, and is eliminated renally (Sargentini-Maier et al., 2007).
- In this study, we collected sparse plasma samples for BRV determination in 2 double-blind, placebo-controlled, phase 2 trials of BRV as add-on treatment of partial onset seizures with the following aims:
  - to build a population pharmacokinetics (PK) model in adult patients with epilepsy;
  - to identify potential demographic covariates;
  - to identify potential drug-drug interaction covariates.

METHODS

- Adult patients with refractory partial onset seizures received adjunctive BRV b.i.d. for 7 to 10 weeks in 2 double-blind, placebo-controlled, parallel-group, dose-ranging studies. The dose levels were placebo, BRV 5, BRV 20, and BRV 50 mg/day (study N01114) and placebo, BRV 50, and BRV 150 mg/day (study N01193) in 2 intakes. There were approximately 50 patients per group.
- Two plasma samples per visit were obtained on 2 to 4 occasions between weeks 3 and 10.
- BRV concentration-time data were modeled by nonlinear mixed-effect modeling using NONMEM with first-order conditional estimation method (FOCE).
- A 1-compartment model with first-order absorption and elimination was used, parameterized as a function of absorption rate constant (K0), clearance (CL), and distribution volume (V).
- Body weight (BW) was included in the base model as an allometric factor of CL and V:

\[
CL = \theta_1 \cdot \left( \frac{BW}{\text{median BW}} \right)^{\theta_2} \quad V = \theta_1 \cdot \left( \frac{BW}{\text{median BW}} \right)^{\theta_2}
\]

- Age, sex, race, concomitant antiepileptic drugs (AEDs), and creatinine clearance (CrCl) were examined as possible covariates to explain interindividual variabilities (IVIV) in PK parameters of BRV.
- Concomitant AED treatments were classified as neutral (no hepatic enzyme-inhibiting/inducing properties), inducer (hepatic inducer alone or in combination with neutral), inhibitor (hepatic inhibitor alone or in combination with neutral), or mixed (combination of inhibitor and inducer).

RESULTS

- 1150 concentration-time measurements and dosing records were available within 12 hours postdose in 254 patients (Figure 1).

![Figure 1. BRV Concentration-Time Observations (µg/mL, normalized to 25 mg/intake)](image)

- Patients were taking 1 or 2 concomitant AEDs (39 neutral, 98 inducer, 77 inhibitor, and 40 mixed).
- Demographic characteristics:
  - Males: 50%
  - Caucasian: 67%, Indian Asians 16%, Hispanics 11%, Blacks 3%, Others 3%
  - Mean BW (range): 70 kg (24-129 kg)
  - Mean age (range): 34 years (16-65 years)
  - Mean CrCl (range): 122 mL/min (39-253 mL/min)
- BRV plasma concentrations were adequately described by the 1-compartment model, without lag time. The residual variability was low (20.0%) (Table 1).
- The population mean for V was 36 L or 0.51 L/kg.
- IVIVs are shown in Table 1.

![Table 1. PK Parameters of BRV From the Final Model](image)

- Population mean of CL was estimated to be $3.63 \pm 0.902 \text{ L/h}$.
- Concomitant intake of enzyme inducing AEDs was a potential drug-drug interaction covariate.
- Predicted exposures were similar to those determined by IVIV in adult patients with epilepsy; Cmax and Cmin were adequately described by the final model (Figure 2).

![Figure 2. BRV Clearance by Concomitant AED Class](image)

- Most of the IVIV in BRV PK in an ethnically diverse population of patients was accounted for by differences in BW and concomitant use of enzyme inducing AEDs.

CONCLUSION

- Since the identified covariates had a moderate influence on PK parameters, BRV is deemed to have a highly predictable exposure in individual subjects.

References