INTRODUCTION

Brivaracetam (BRV) ((2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide) is a new drug under clinical development for the treatment of epilepsy and neuropathic pain. The aim of this analysis was to describe the population pharmacokinetic profile of BRV in healthy and epileptic adults, and to assess the effect of demographic covariates and concomitant use of AEDs.

METHODS

Study design
This was a retrospective population analysis based on 12 clinical studies conducted in young healthy, renally impaired, elderly volunteers and in epileptic patients populations.

Data analysis
- Database consisted of demographic information and concentration-time records from single and repeated open b.i.d. administration studies (3 days to 4 weeks) in young and elderly healthy subjects, subjects with severe renal impairment, and epileptic patients.
- In total, 4,277 plasma concentration measurements from 203 subjects were used.
- Population PK analysis was performed by non-linear mixed effects modeling using NONMEM Version V, with double precision and first order conditional estimation (FOCE).
- The structural model was a 1-compartment, open model with first order absorption and elimination rates (Subroutine ADVAN 2 TRANS2), using the parameters: - KA: absorption rate constant - CL/F: apparent body clearance - V/F: apparent volume of distribution
- Residual variability was modeled by a proportional error model.
- Individual variability (IV) was modeled on each PK parameter
- Reliability residuals was modeled by a proportional error model.
- Modeling was performed on log-transformed concentrations
- Investigated covariates:
  - Food on KA
  - Age, weight, BSA, gender, ethnicity, CLcr, concomitant AEDs, dose, duration of treatment, health status on CL/F
  - Age, weight, BSA, gender, ethnicity, dose and duration of treatment on V/F
- Simulations in different subject sub-populations were undertaken to evaluate the clinical significance of covariates significantly affecting the PK parameters.

RESULTS

Subjects
- Population demographic characteristics are summarized in Table 2.
- Subjects with epilepsy were chronically treated with 1-3 concomitant AEDs, classified as neutral, inducer or inhibitor

Table 2. Demographic characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate [95% CI]</th>
<th>Inter-individual variability %</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA fasting conditions, h&lt;sub&gt;i&lt;/sub&gt;</td>
<td>4.65 [2.45-9.61]</td>
<td>6.8 2</td>
</tr>
<tr>
<td>KA fed conditions, h&lt;sub&gt;i&lt;/sub&gt;</td>
<td>0.017 [0.751-12.8]</td>
<td>15.1</td>
</tr>
<tr>
<td>CL/F typical value, L/h</td>
<td>0.812 [0.736-0.888]</td>
<td>0.198 [0.151-0.262]</td>
</tr>
<tr>
<td>Age factor</td>
<td>0.0022 [0.0000-0.0045]</td>
<td></td>
</tr>
<tr>
<td>Age correlation factor</td>
<td>0.0000 [0.0000-0.0000]</td>
<td></td>
</tr>
<tr>
<td>Gender factor</td>
<td>0.0001 [0.0000-0.0001]</td>
<td></td>
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<tr>
<td>V/F typical value, L</td>
<td>0.16 [0.14-0.18]</td>
<td></td>
</tr>
<tr>
<td>Weight factor</td>
<td>0.0074 [0.0046-0.012]</td>
<td></td>
</tr>
<tr>
<td>Gender factor</td>
<td>0.010 [0.008-0.012]</td>
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</tbody>
</table>

Effect of Covariates
- Post-hoc estimates of KA under fasting and fed conditions are shown in Figure 3.
- Post-hoc estimates of CL/F versus age (males not under concomitant AEDs), bodyweight (males not under concomitant AEDs), gender and concomitant inducer AEDs are shown in Figure 3.
- Post-hoc estimates of V/F versus bodyweight (male subjects) and gender are shown in Figure 4.

Figure 3. Boxplot of post-hoc individual estimates of CL/F vs age, bodyweight, gender and concomitant inducer AEDs

Figure 4. Post-hoc estimates of V/F vs bodyweight and gender

CONCLUSIONS

A large part of the inter-individual variability in brivaracetam pharmacokinetics was accounted for by differences in weight, gender, age and concomitant enzyme-inducing AEDs.

Since the identified covariates had a modest influence on PK parameters, brivaracetam is deemed to have a highly predictable exposure in individual subjects. No dose adjustment is required.

The current model can be used to predict exposure in target populations in phase 2/3 studies.

Population pharmacokinetics of the new antiepileptic drug Brivaracetam

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