Population Pharmacokinetics of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Modafinil is currently being evaluated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. In children, plasma modafinil concentrations were linearly related to weight based on the allometric model with induction of CL/F adequately fit the pooled sparse data from Phase 3 studies and 666 concentrations from 24 patients in the typical value approach. Half-life for the youngest patients (age 6) was 6 to 7 hours, and 9 to 10 hours for the oldest patients (age 7). Half-life relationships were nonlinear, and was greater than 15 hours. Weight-based maximum doses were targeted for patients ≤30 kg (340 mg) and >30 kg (425 mg) in one Phase 3 study. Covariate models were evaluated: age, body mass index (BMI), weight, and gender. The influence of ethnicity, dose/kg, and the mean sulfone metabolite concentration was not significant. Weight-based dosing strategy achieved target exposure, with the main factors responsible for the difference in pharmacokinetics in children and adolescents are age and weight, with no additional correlation to sex, race, or other demographic factors.

RESULTS

• The pharmacokinetic properties of modafinil do not appear to change after 18–21 months of dosing.
• The mean sulfone metabolite concentration was not significant.
• Diagnostic plots of the change in parameter value (individual Bayesian estimates) and weighted residuals versus time since last dose were examined.
• The estimated half-life of the typical patient was 15 hours.
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Figure 1. Flowchart of Population Pharmacokinetic Study

Population Pharmacokinetic Model

Development and Evaluation of the Pharmacokinetic Model

Model Development

A two-compartment model with an absorption lag (CL/F = CL/F0) and apparent oral clearance (CL/F = CL/F0) modeled as a function of body weight (kg) and age (y) was used to model the pooled sparse data from Phase 3 studies and 666 concentrations from 24 patients in the typical value approach. Half-life for the oldest patients (age 7) is around 9 to 10 hours. This shift in half-life appears to occur between 9 and 11 years of age.

The structure of the final model is shown in Figure 1. The final population pharmacokinetic model is based on the allometric model with induction of CL/F adequately fit the pooled sparse data from Phase 3 studies and 666 concentrations from 24 patients in the typical value approach. The final model is shown in Figure 2.

Model Validation

• Predictive performance of the Phase 2 model was evaluated using a leave-one-subject-out cross-validation approach. The mean absolute error (MAE) was used as a measure of prediction for individual patients. 
• The model fit the data well, with the mean absolute error (MAE) was used as a measure of prediction for individual patients. 
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Figure 2. Distributions of Weighted Residuals From Final Model With Induction of CL/F in Pooled Phase 2 Data From Studies 2, 3, and 4

Table 3. Prediction Errors for the Final Model in the Pooled Phase 2 Data From Studies 2, 3, and 4

<table>
<thead>
<tr>
<th>Parameter Mean</th>
<th>SEM</th>
<th>Estimate Variability (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/hr)</td>
<td>29.2</td>
<td>0.5</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>4.0</td>
<td>0.6</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>30.5</td>
<td>0.7</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>19.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

• The main factors responsible for the difference in pharmacokinetics in children and adolescents are age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 3. Distributions of Weighted Residuals From Final Model With Induction of CL/F in Pooled Phase 2 Data From Studies 2, 3, and 4

CONCLUSIONS

• Once steady-state DL is reached, the pharmacokinetic properties of modafinil are apparent and no further increase in drug levels is expected after long-term dosing.

Figure 4. Observed and Individual-Predicted Modafinil Concentrations for Base-Case One-Compartment Model With Weight on CL/F in Patients 2 Weeks and >40 Weeks of Dosing

Table 2. Parameter Estimates and Percent Standard Error of the Typical Value of Modafinil Film-Coated Tablets in Patients Following 2 Weeks and >40 Weeks of Dosing

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• The estimated half-life of the typical patient was 15 hours.

Figure 5. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

The results of this study are that the half-life of the typical patient is not significantly affected by age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 6. Estimated Half-Life of Modafinil Versus Patient Age

The model described the apparent oral clearance and apparent volume of distribution as functions of body weight and age. The apparent oral clearance (CL/F) is directly proportional to body weight and is a function of body weight. The apparent volume of distribution (V/F) is inversely proportional to body weight.

Figure 7. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

The results of this study are that the half-life of the typical patient is not significantly affected by age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 8. Estimated Half-Life of Modafinil Versus Patient Age

The model described the apparent oral clearance and apparent volume of distribution as functions of body weight and age. The apparent oral clearance (CL/F) is directly proportional to body weight and is a function of body weight. The apparent volume of distribution (V/F) is inversely proportional to body weight.

Figure 9. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

The results of this study are that the half-life of the typical patient is not significantly affected by age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 10. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

The results of this study are that the half-life of the typical patient is not significantly affected by age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 11. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

The results of this study are that the half-life of the typical patient is not significantly affected by age and weight, with no additional correlation to sex, race, or other demographic factors.

Figure 12. Model Predicted AUC/O for 48 kg Patient With DL of 150 mg

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