

## Retrospective population pharmacokinetic analysis of levetiracetam in Western and Japanese adults

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**Background and Objective:** Levetiracetam (LEV), a second-generation antiepileptic drug (AED) indicated for the adjunctive treatment of partial-onset epilepsy, has been shown to possess a favourable pharmacokinetic profile.<sup>1</sup> It is well recognised that all drugs exhibit inter-subject variability in pharmacokinetics and that such differences vary considerably among individual drugs and are dependent on a range of factors. One such potential factor is ethnicity.<sup>2</sup> The aim of this investigation was to assess the sensitivity of LEV pharmacokinetics to ethnicity and other demographic characteristics using 2 sets of similar studies conducted in Western and Japanese adults.

**Methods:** Data were pooled from 2 sets of 5 matched studies conducted in Europe or in the USA and in Japan, respectively, in which LEV was administered (250-5,000 mg) orally to healthy subjects and patients with epilepsy. In total, 5,408 plasma concentration measurements were available from 524 individuals participating in 6 Phase I, 2 Phase III and 2 long-term safety studies of add-on LEV. A 1-compartment open model with 1st order absorption and elimination was used for population non-linear mixed effects modelling (NONMEM). The model was parameterised as a function of clearance (CL/F), distribution volume and absorption rate constant. Inter-subject variability on the parameters was described by a proportional error model, and residual variability by 2 distinct proportional error models for patients and for healthy subjects, respectively. An inter-occasion variability was used for absorption rate constant.

**Results:** Ethnicity had no statistically significant effect in the presence of other covariates. Body weight, gender, creatinine clearance and concomitant (1-3) AEDs significantly affected CL/F. Body weight, disease and concomitant valproic acid significantly affected distribution volume. CL/F varied by a maximum of 20% when body weight was halved or doubled from the population mean, and was 10% lower in females than males. In addition, CL/F was increased 9% by enzyme inducers and decreased 19% by valproic acid. Distribution volume increased linearly with body weight, and decreased 23% with valproic acid. LEV exposure (AUC) was 12% higher in females than males. Decreasing body weight from 70 to 40 kg was predicted to increase exposure by 16%, and halving creatinine clearance to increase exposure by 10%. Exposure was reduced 8% by enzyme inducers and increased 23% by valproic acid; the latter effect was assumed to be through the established association between valproic acid and increased body fat.

**Conclusions:** This retrospective population analysis suggests the absence of ethnic differences in pharmacokinetics of LEV between Western and Japanese, other than those arising from body weight differences. Small differences seen among individual demographic characteristics and concomitant AED types are likely to be of limited clinical significance. Consequently, dose adjustment should usually not be necessary, given the large safety margin of LEV and the individualised dose approach recommended for LEV.

### References

1. Patsalos PN. Pharmacokinetics profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* 2000; 85: 77-85.
2. Bjornsson TD, Wagner JA, Donahue SR, *et al*. A review and assessment of potential sources of ethnic differences in drug responsiveness. *J Clin Pharmacol* 2003; 43: 943-67.