Adjunctive Pregabalin vs. Gabapentin for Focal Seizures: interpretation of Comparative Outcomes

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Supplemental Materials

Figure e-1. Modeling of pregabalin and gabapentin dose vs % change in seizure frequency in patients with POS requiring adjunctive therapy.

The initial study concept was based on modelling by Dr Jaap Mandema of Quantitative Solutions, Menlo Park, CA (see http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s2-2-QuantitativeSolutionsMandema.ppt, accessed Oct 31 2014). The objective of this modelling was to quantify the dose-response relationship of a number of antiepileptic drugs in patients with refractory epilepsy, which included the a2d ligands gabapentin and pregabalin. The efficacy endpoints included median % reduction in seizure frequency, and the proportion of patients with 50% or greater reduction in seizure frequency (responders). The comparison of the median % reduction in seizure frequency is presented in this publication.

To create the model, clinical trials were included if they were randomized, controlled trials investigating add-on treatment with any of the above listed compounds; they recruited patients with...
partial epilepsy refractory to one to three AEDs; they were parallel studies or crossover studies for which data from the first treatment period was available; treatment was continued for at least twelve weeks; and results were reported which included seizure frequency.

The model for seizure frequency was well described by an E\textsubscript{max} model:

$$g(Y_{ij}) = g\left\{E_0 + \frac{E_{\text{max}} \cdot \text{Dose} + \eta_j}{\text{Dose} + \text{ED}_{50}}\right\} + \omega_j$$

$$g(x) = \log(x/100 + 1)$$

where

- $Y_{ij}$ represents the percent change in seizure frequency from pre-treatment values of the $i^{th}$ subject in the $j^{th}$ trial;
- $E_0$ is the placebo response;
- $E_{\text{max}}$ is the maximal drug effect, reflecting the maximal difference in response between placebo and active treatment;
- Dose is the dose in mg/day;
- ED\textsubscript{50} is the dose to achieve 50% of E\textsubscript{max};
- $\eta_j$ is a trial specific random effect assumed to be normally distributed with variance $\omega^2$;
- $\varepsilon$ reflects the between subject variability assumed to be normally distributed with variance $\sigma^2$; and
- $g\{x\}$ is the log of the reduction ratio

Dependency of model parameters on other variables was evaluated using a likelihood ratio test. There was no significant residual heterogeneity, no significant random trial effect on E\textsubscript{max}, and validated the use of placebo as an internal reference. The analysis suggested that the clinical data for the evaluated AEDs were consistent with a model that assumed a common dose response relationship for all compounds (same E\textsubscript{max} and $\eta$) with the only difference being the potency, i.e. the dose required to produce a certain effect.

The studies included in the modelling included gabapentin studies 945-210P, 945-005, 945-006, 945-009/010; and pregabalin studies 1008-009, 1008-011, 1008-034.