

## Clinical Pharmacology/Biopharmaceutics Review

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|-------------------------|---------------------------|
| PRODUCT (Generic Name): | Divalproex Sodium         |
| PRODUCT (Brand Name):   | DEPAKOTE                  |
| DOSAGE FORM:            | ER Tablets                |
| DOSAGE STRENGTHS:       | 250 mg and 500 mg         |
| NDA:                    | 20-782, 21-168 (SLR-004)  |
| NDA TYPE:               | Response to NA letter     |
| SUBMISSION DATE:        | 6/26/02, 8/7/02, 11/13/02 |
| SPONSOR:                | Abbott Laboratories Inc.  |
| REVIEWER:               | Veneeta Tandon, Ph.D.     |
| TEAM LEADER:            | Ramana Uppoor, Ph.D.      |
| OCPB DIVISON:           | DPE I, HFD 860            |
| OND DIVISION:           | HFD 120                   |

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**Study M01-274:** .....*Comparison of the bioavailability of Depakote ER formulation relative to Depakote DR formulation in adult patients with epilepsy on the Depakote DR formulation and an enzyme inducing antiepileptic drug.* ..... 28

### **EXECUTIVE SUMMARY**

This application intends to support the conversion of Depakote DR to Depakote ER if the Depakote ER doses are 8-20% higher than that of Depakote DR tablets. A dose conversion table is provided in the label for conversion from Depakote DR to Depakote ER tablets based on the results from the two studies submitted in this application.

### **RECOMMENDATION**

NDA 20-782 is acceptable from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics provided the DSI inspection results are acceptable. For the conversion from Depakote DR to Depakote ER, the adequacy of data beyond a DR dose of 3000 mg cannot be established from a pharmacokinetic point of view as only 4 subjects were enrolled at DR doses greater than 3000 mg. This judgement is deferred to the reviewing Medical Officer.

Labeling changes recommended on pages 14-16 of the review should be conveyed to the sponsor.

Labeling comment on page 17 should be conveyed to the Medical Officer.

Veneeta Tandon, Ph.D.  
Pharmacokineticist  
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. \_\_\_\_\_

## OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

### QUESTION BASED REVIEW

#### Background Information:

The original NDA for Divalproex extended release formulation (Depakote ER) filed in June 1997 was found unacceptable for the treatment of Epilepsy. The NDA was solely based on BE studies and no clinical trials were conducted to show efficacy of Depakote ER for the treatment of Epilepsy. The original NDA consisted of two bioequivalence studies comparing the Depakote ER to the Depakote DR formulation at equal doses. One study was conducted in healthy volunteers (Study M95-376) that did not receive concomitant antiepileptic drugs (AEDs) and ER formulation was given under fed and fasted state and the DR formulation under fasted state. The second study (Study M95-401) was performed in patients with epilepsy with concomitant AEDs and all treatments given in fed state.

Results from the previous study in healthy subjects indicated that the AUC of ER and DR formulations were equivalent, C<sub>max</sub> and C<sub>mins</sub> were lower for the ER formulation and 90% CI did not fall within the acceptable bioequivalence limits under fasted conditions. Lower C<sub>mins</sub> indicated unacceptable product performance. The study in patients with epilepsy with concomitant AEDs demonstrated that the ER formulation was equivalent with respect to AUC, C<sub>max</sub> and C<sub>min</sub> to the DR formulation given QID at the same total daily dose under fed conditions. These studies do not suggest the equivalency of Depakote ER when used as monotherapy. In addition, since BE study was shown only in fed state, equivalence cannot be concluded (fasting state being the current regulatory standard). Hence, under such circumstance, if converted to ER formulation, the patients would be effectively underdosed.

These previous studies were conducted at equidoses of the DR and ER formulations of Depakote. From previous pharmacokinetic studies it was established that an increase in the ER dose of 8-20% would provide equivalence in the AUC relative to the Depakote DR, since the AUC, C<sub>max</sub> and C<sub>min</sub> were lower by 8-20% with the ER formulation. Ratios of the ER doses to DR doses in the range of 1.08-1.20 should allow the ratios of central values to fall within the value of 0.8-1.25 required for establishing bioequivalence by AUC. A range of 8-20% had to be used, as the ER tablet is only available in 250 mg and 500 mg strengths, where as the DR tablet is available in 125, 250 and 500 mg strength. This application intends to support the conversion of Depakote DR to Depakote ER if the Depakote ER doses are 8-20% higher than that of Depakote DR tablets. A dose conversion table is provided in the label for conversion from Depakote DR to Depakote ER tablets based on the results from the studies submitted in this application.

**With the present studies can the equivalency of the Depakote ER formulation to that of the Depakote DR formulation be determined?**

In response to the non-approval letter for NDA 20-782, the sponsor has conducted two multiple dose comparative bioavailability studies with the ER and DR formulations, one study (M00-232) in healthy subjects and the second study (M01-274) in patients with epilepsy taking concomitant AEDs. The study designs for these studies were discussed at length in meetings with the agency prior to conduct of the studies.

In both studies Depakote ER formulation taken QD was found equivalent to Depakote DR formulation taken BID or TID in terms of AUC, Cmax and Cmin at ER doses 8-20% higher than that of the DR formulation. In both studies the ER regimen was administered under fasting conditions, the morning DR regimen was also given under fasted condition, however, the latter doses were given under modified fasting conditions.

The following Table shows the results based on agency's bioequivalence criteria. Two one-sided test was performed on log transformed AUC. For Cmax and Cmin one-sided test was performed on log transformed Cmax and untransformed Cmin. The reviewer calculated log transformed 90% CI on all parameters and is reported in this Table as well. The doses evaluated are given in the Table below.

**Healthy Subjects:**

| Regimens<br>T vs R  | Parameter | Central<br>Value*<br>Test<br>(T) | Central<br>Value*<br>Reference<br>(R) | Point<br>Estimate**            | Upper/Lower<br>95%<br>confidence<br>bound | 90% CI      |
|---|-----------|----------------------------------|---------------------------------------|--------------------------------|---|-------------|
| 1000 mg ER vs.<br>875 mg DR<br>(N=35)                                       | AUC24     | 1923                             | 1887                                  | 1.019                          | -   | 0.966-1.075 |
| 1500 mg ER vs.<br>1250 mg DR<br>(N=33)                                      | AUC24     | 2393                             | 2170                                  | 1.103                          | -   | 1.068-1.139 |
| 1000 mg ER vs.<br>875 mg DR<br>(N=35)                                       | Cmax      | 94.01                            | 110.2                                 | 0.853                          | 0.892                                     | 0.814-0.892 |
| 1500 mg ER vs.<br>1250 mg DR<br>(N=33)                                      | Cmax      | 114.6                            | 125.3                                 | 0.914                          | 0.939                                     | 0.889-0.939 |
| 1000 mg ER vs.<br>875 mg DR<br>(N=35)                                       | Cmin      | 65.32                            | 59.11                                 | 1.105+<br>range<br>(0.53-1.96) | 1.014                                     | 0.997-1.198 |
| 1500 mg ER vs.<br>1250 mg DR<br>(N=33)                                      | Cmin      | 82.37                            | 66.11                                 | 1.246+<br>range<br>(0.71-1.86) | 1.164                                     | 1.157-1.330 |
| * Antilogarithm of the least square means for logarithms                    |           |                                  |                                       |                                |   |             |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                                  |                                       |                                |   |             |
| + Ratio (T/R) of the least square means                                     |           |                                  |                                       |                                |   |             |

The results show that:

- **For AUC24:** Both 1000 mg ER/875 mg DR regimen and 1500 mg ER/1250 mg DR regimen are equivalent in terms of AUC as the 90% CI are within the acceptable bioequivalence limits.

- **For C<sub>max</sub>:** Both 1000 mg ER/875 mg ER regimen and 1500 mg ER/1250 mg DR regimen are equivalent in terms of C<sub>max</sub> as the protocol specified one-sided 95% upper confidence bound for the ratio of the C<sub>max</sub> central values were lower than 1.25. The 90% CI calculated by the reviewer was also within the acceptable limits.
- **For C<sub>min</sub>:** Both 1000 mg ER/875 mg regimen and 1500 mg ER/1250 mg DR regimen are equivalent in terms of C<sub>min</sub> as the protocol specified one-sided 95% lower confidence bound for the ratio of the C<sub>min</sub> central values were higher than 0.80. The 90% CI calculated by the reviewer was also within the acceptable limits for the 1000 mg ER regimen, but higher for the 1500 ER regimen. But as long as the C<sub>min</sub> is higher for the ER regimen, compared to the DR regimen, it is not likely to be of concern for reduced efficacy from the ER formulation.
- Looking at individual C<sub>min</sub> values for 1000 mg ER/875 mg DR mg, it was observed that 7 out of 35 subjects had C<sub>min</sub> ratios lower than 0.8. The ratios were 0.62 (#101), 0.70 (#102), 0.53 (#103), 0.60 (#110), 0.79 (#119), 0.74 (#122) and 0.72 (#123). For 1500 mg ER/1250 mg DR regimen, only 2 subjects had C<sub>min</sub> ratios lower than 0.8, values being 0.71 (#107) and 0.74 (#110). Looking at the 24 hour profile of these subjects it was observed that the ER regimen has lower concentrations at all time points (See page 24). Although, the C<sub>min</sub> ratios were lower in these subjects, the individual C<sub>min</sub> values were comparable to the distribution of the C<sub>min</sub> values in the entire population, as shown in the Box plot on page 26. Subject 110 was the only subject that showed a lower C<sub>min</sub> value of the ER formulation at both dosing regimens (1000 and 1500 mg ER). The others could be attributed to the population variability.

The individual C<sub>min</sub> values were looked at closely because the sponsor stated in the proposed label that plasma valproate C<sub>min</sub> concentrations on average are equivalent but may vary across patients. Also stated that if satisfactory clinical response is not obtained, plasma concentrations should be measured to see whether they fall in the therapeutic range. This had raised some concerns during the filing meeting, hence, the number of subjects that had low C<sub>mins</sub> were looked at closely.

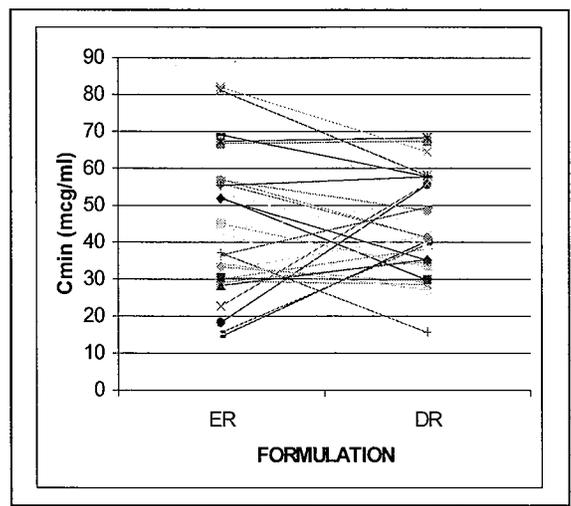
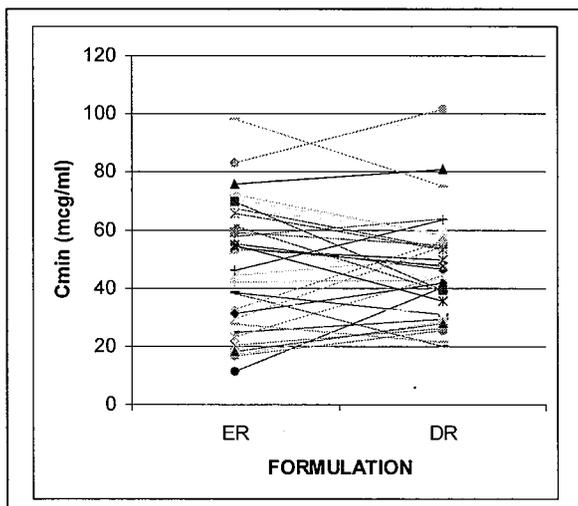
***In patients with epilepsy with concomitant AEDs:***

In this study patients were given a range of ER doses from 1000-5000 mg, with corresponding 8-20% lower DR doses. Statistical analysis based on all subjects on various doses pooled together showed equivalence based on agency's bioequivalence criteria, as shown in the following Table:

| Regimens<br>T vs R  | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference (R) | Point<br>Estimate**           | Upper/<br>Lower<br>95%<br>confidence<br>bound | 90% CI          | p-value |
|---|-----------|-------------------------------|------------------------------------|-------------------------------|---|-----------------|---------|
| ER QD vs.<br>DR Q8H<br>(N=64)   | AUC24     | 1551                          | 1539                               | 1.008<br>range<br>(0.87-1.05) |   | 0.964-<br>1.055 | 0.7575  |
| ER QD vs.<br>DR Q8H<br>(N=64)   | Cmax      | 83.27                         | 92.59                              | 0.899<br>range<br>(0.82-1.09) | 0.938   | 0.864-<br>0.938 | 0.0001  |
| ER QD vs.<br>DR Q8H<br>(N=64)   | Cmin      | 45.85<br>range<br>(20.1-98.2) | 44.82<br>range<br>(15.5-101.4)     | 1.022<br>range<br>(0.28-2.40) | 0.950+  | 0.888-<br>1.06  | 0.6149  |
| * Antilogarithm of the least square means for logarithms                    |           |                               |                                    |                               |   |                 |         |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                               |                                    |                               |   |                 |         |
| + Ratio (T/R) of the least square means                                     |           |                               |                                    |                               |   |                 |         |

The results show that:

- **For AUC:** The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of AUC, as the 90% CI on log transformed data was within the acceptable limits
- **For Cmax:** The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of Cmax, as the protocol specified criteria of one-sided 95% upper confidence bound for the ratio of the Cmax central values were lower than 1.25 and the 90% CI calculated by the reviewer was also within the acceptable limits.
- **For Cmin:** The ER QD regimen is equivalent to the DR TID regimen at the evaluated doses in terms of Cmin one-sided 95% lower confidence bound for the ratio of the Cmin central values on untransformed Cmin were greater than 0.8. The 90% CI on log transformed Cmin values calculated by the reviewer were also within the acceptable limits. The stick plot for individual subject Cmin values for the ER and DR regimen is given below.



- Looking at individual data it was observed that six subjects had more than 2-fold lower C<sub>min</sub> for the ER regimen as compared to the DR regimen and 14 subjects (excluding the 6) had > 20% lower C<sub>min</sub> in the ER regimen as compared to the corresponding DR regimen. The low C<sub>min</sub> subjects did not belong to any particular dose group or to any particular group of patients taking the same concomitant AEDs. Although, some subjects have lower C<sub>min</sub> values for the ER formulation, they were within the population distribution of the C<sub>min</sub> values for Reference or Test, as shown by the distribution in C<sub>min</sub> values in the box plot on page 35. If adequate clinical response is not obtained, it would be desirable to monitor plasma valproate levels.

The individual C<sub>min</sub> values were looked at closely because the sponsor stated in the proposed label that plasma valproate C<sub>min</sub> concentrations on average are equivalent but may vary across patients. Also stated that if satisfactory clinical response is not obtained, plasma concentrations should be measured to see whether they fall in the therapeutic range. This had raised some concerns during the filing meeting, hence, the number of subjects that had low C<sub>mins</sub> were looked at closely.

**Have appropriate doses been evaluated to assess the bioequivalence of the ER formulation to that of the DR formulation for conversion from the DR to the ER regimen?**

The recommended initial dose for Depakote DR for the treatment of epilepsy is at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. Hence, for the approval of Depakote ER for the treatment of epilepsy, the above doses should be evaluated.

Study M00-232 in healthy volunteers was conducted at dose levels of 1000 mg ER/875 mg DR and 1500 mg ER/1250 mg DR. The DR doses were given BID in divided doses. This study does not evaluate the higher maintenance doses and only evaluates DR doses given BID. This may not be able to describe the adequacy for the equivalence of Depakote ER to the DR tablets, when the DR tablets are administered TID or QID.

Both these concerns have been addressed by the sponsor in Study M01-274 in patients with epilepsy, where a Depakote DR dose range of 875-4250 mg has been compared to a corresponding 8-20% increase in the ER dose (1000-5000 mg). This covers a DR dose range up to 60 mg/kg/day. However, the total number of subjects evaluated at each dose increment is given below:

| DR Dose | Number of Subjects | DR Dose | Number of Subjects |
|---------|--------------------|---------|--------------------|
| 875 mg  | 10                 | 2500 mg | 4                  |
| 1250 mg | 11                 | 3000 mg | 8                  |
| 1375 mg | 4                  | 3500 mg | 1                  |
| 1750 mg | 16                 | 4000 mg | 2                  |
| 2125 mg | 3                  | 4250 mg | 1                  |
| 2250 mg | 4                  |         |                    |

As we can see from the above table there are very few subjects (N=4) enrolled at doses higher than 3000 mg. From PK standpoint a total of 4 subjects at DR doses greater than 3000 mg may not be adequate to assess the equivalence of the DR and ER regimen for doses >3000-5000 mg.

The sponsor's survey from the Physicians Drug and Diagnosis Audit (PDDA), estimated that 80% of the adult epilepsy patients with another AED received daily doses of 2000 mg/day or less. An efficacy and safety trial (Study M88-194) conducted by the sponsor to support approval in complex partial seizures indicated that 62% of the subjects had an average daily dose in the maintenance period of 2500 mg or less, although doses up to 6000 mg/day (=91.2 mg/kg/day) were used. There were 90% subjects who averaged less than 4000 mg/day, seven subjects averaged more than 4000 mg/day (=60 mg/kg/day). The maximum epilepsy dose in the current labeling is 60 mg/kg/day.

Based on these historical data there are 20-40% of the subjects taking Depakote doses greater than 2000 mg/day. Study M01-274 in patients with epilepsy has enrolled fewer subjects at doses greater than 2000 mg/day. The dose of 3000 mg/day does seem to have adequate number of subjects, but the other doses have subjects ranging from 1-4. The adequacy of the number of subjects at the higher doses of Depakote needs to be evaluated by the reviewing Medical Officer.

**Is the Sponsor's rationale for studying total concentrations of valproic acid acceptable, given the nonlinear protein binding?**

The sponsor has developed an equation describing the relationship between total and free concentrations of valproic acid.

Free valproic acid plasma concentrations were calculated from the total concentration for each sample using the following equation (based on data from Study M98-938; NDA 20-593, S-006), where the % free valproate increases from about 10% at total concentrations of 50 µg/ml to 19% at total concentrations of 150 µg/ml.

$$C_{\text{Free}} = 0.0009.C_{\text{Total}}^2 + 0.0527.C_{\text{Total}}$$

Using this equation it was found out that the predicted free concentrations were not different from those derived from the analysis of total valproate levels.

For comparison of DR and ER regimens, if AUC are similar, then the two regimens should produce similar average total concentration ( $C_{\text{avg}} = \text{AUC}/24$ ). Therefore, if the average total concentrations are similar, then average free concentrations and exposure to free drug should be similar and equivalent, irrespective of nonlinear protein binding.

The above equation was based on a range of concentrations, with the upper range being 150 µg/ml. The highest concentration of 163 µg/ml was observed in one subject with the 3500 mg DR dose. All other subjects at all doses had concentrations less than 150 µg/ml. Using the above equation, the ER/DR  $C_{\text{max-free}}$  ratio would be 0.83, which is smaller than the ER/DR  $C_{\text{max-total}}$  ratio of 1.11 in this subject. Hence, although the concentration is outside the validated range in this subject, the argument of total concentrations giving the same result as free concentration still holds true.

At the highest DR dose of 4250 mg, the maximum concentration observed was 122 µg/ml. Hence, the sponsor's equation establishing the relationship of total and free concentrations can be applied to all doses.

It is therefore acceptable to evaluate total concentrations of valproic acid.

**Was there an effect of Depakote DR dose on the Depakote ER/DR relative bioavailability?**

The frequency of the Depakote doses is given in the previous Table. To investigate whether the bioavailability of the Depakote ER formulation relative to that of the Depakote DR Q8H changed with the Depakote DR dose, two approaches were taken by the sponsor:

1. A regression analysis conducted on the ratio of dose normalized ER AUC24 to DR AUC24 value showed that the bioavailability of Depakote ER relative to Depakote DR was independent of the total daily Depakote DR dose ( $p= 0.3041$ )
2. An analysis conducted on the natural logarithm of dose normalized AUC24 using an ANOVA after collapsing the total daily DR dose groups in the study into several larger dose groups showed that the point estimates for ER/DR relative bioavailability were greater than 0.8 for all dose groups . The dose groups were:
  - i) Low: 875 mg DR; N=10
  - ii) Low intermediate: 1250-1375 mg DR; N=15
  - iii) Intermediate: 1750 mg DR; N=15
  - iv) High intermediate: 2000-2500 mg DR; N=12
  - v) High: 3000-4250 mg DR, N=12

The ER/DR relative bioavailability as given by the point estimate and the p-value is given in the following Table

| Parameter                       | Point Estimate<br>ER/DR Relative<br>Bioavailability | p-value |
|---------------------------------|---|---------|
| ER/DR: 875 mg dose group; N=10  | 0.99  | 0.8193* |
| ER/DR: 1250 mg dose group; N=15 | 0.80  | 0.0001* |
| ER/DR: 1750 mg dose group; N=15 | 0.84  | 0.0016* |
| ER/DR: 2250 mg dose group; N=12 | 0.96  | 0.5368* |
| ER/DR: 3500 mg dose group; N=12 | 0.85  | 0.0094* |

|                       |  |        |
|-----------------------|--|--------|
| ER/DR: Linear trend   |  | 0.5764 |
| ER/DR: 3500 vs 875 mg |  | 0.1010 |

\*for ER AUC vs DR AUC

- The primary test for dose group and regimen interaction was not statistically significant (p=0.0645)
- A secondary test comparing the ER/DR relative bioavailability between the lowest (875 mg) and highest (3000 mg) DR dose groups was also not statistically significant (p=0.1010).
- A test for linear trend with Depakote DR dose on the ER/DR relative bioavailability was also not statistically significant (p=0.5764)
- The least square mean point estimates of ER/DR relative bioavailability of dose normalized AUC ratios for the different Depakote DR dose groups were 0.99, 0.80, 0.84, 0.96 and 0.85 for above 5 dose groups respectively.
- Looking at individual Cmins no trend was observed between dose group and low Cmins for the ER regimen.

**What was the effect of concomitant antiepilepsy drugs (AED) in patients when converting from Depakote DR to Depakote ER regimen?**

Concomitant AEDs are known to induce hepatic microsomal enzymes and may thus reduce systemic bioavailability of valproate. No specific trends could be determined in the PK parameters (AUC, Cmax and Cmin) based on coadministered AEDs. The AEDs evaluated were Carbamazepine (N=15), Topiramate (N=5), Phenobarbital (N=4), phenytoin (N=28), Lamotrigine (N=11) and Primidone (N=1). Oxcarbazepine was not evaluated.

The concomitant AED dose, frequency and the point estimate for the ER/DR relative bioavailability is shown in the following Table.

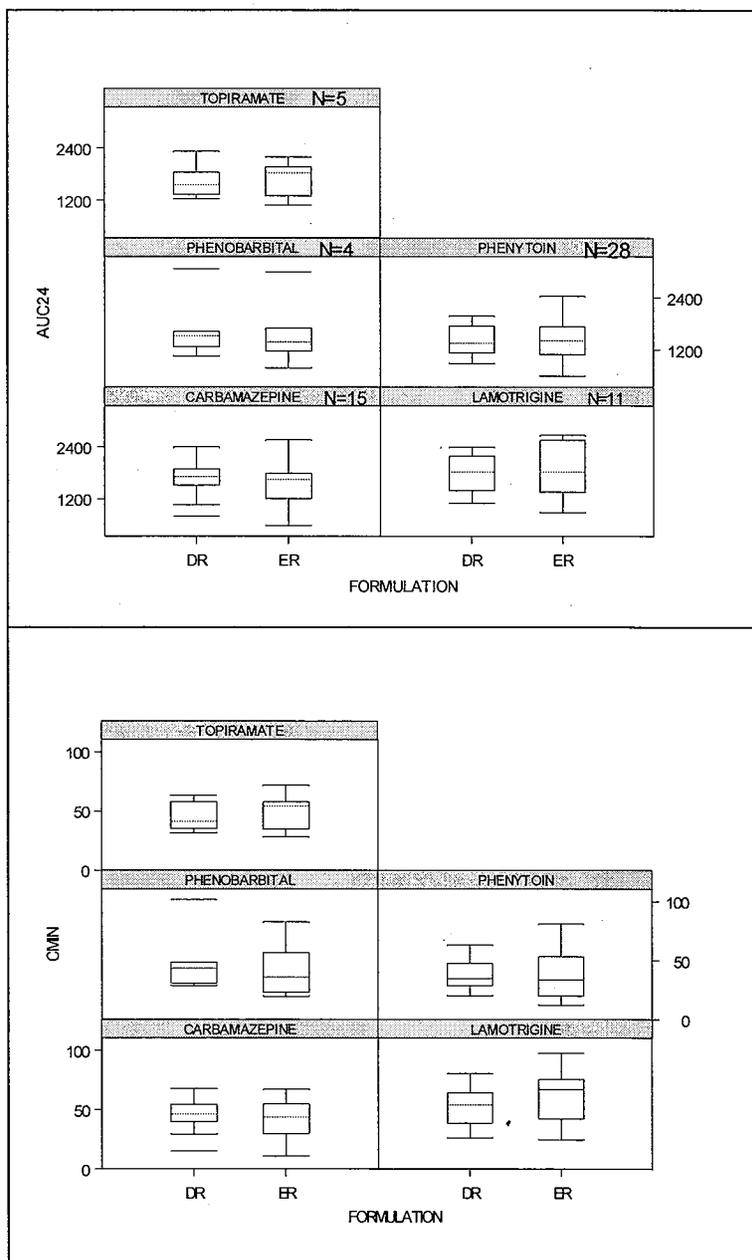
| AED           | Point Estimate | p-value | Dose (mg/day) |      | AED Concentration (µg/ml) |     | Frequency | Percent |
|---------------|----------------|---------|---------------|------|---------------------------|-----|-----------|---------|
|               |                |         | Min           | Max  | Min                       | Max |           |         |
| Carbamazepine | 0.79           | 0.0001  | 200           | 1500 |                           |     | 15        | 23.4    |
| Lamotrigine   | 0.93           | 0.2432  | 50            | 400  |                           |     | 11        | 17.2    |
| Phenobarbital | 0.87           | 0.1493  | 120           | 250  |                           |     | 4         | 6.3     |
| Phenytoin     | 0.89           | 0.0047  | 150           | 600  |                           |     | 28        | 43.8    |
| Primidone     |                |         | 1000          | 1000 |                           |     | 1         | 1.6     |
| Topiramate    | 0.96           | 0.6782  | 100           | 400  |                           |     | 5         | 7.8     |

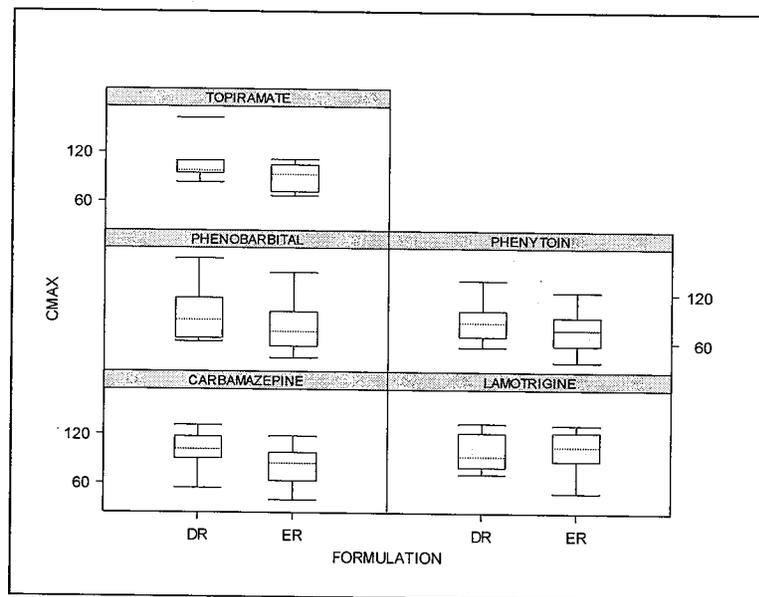
\*There was one subject of primidone, the subject was classified as a phenobarbital-user since primidone is metabolized to phenobarbitone after absorption.

Any particular trend is not likely to be observed, as the same enzyme inducing effect of the AED would be anticipated in both ER and DR regimen. Looking at the individual Cmin it was found that out of the 20 subjects that had lower Cmin values, 10 were on phenytoin, 5 on carbamazepine, 2 on lamotrigine, 2 on phenobarbital, and 1 on

topiramate. Further, in this kind of study, it is very difficult to separate the various factors affecting the relative bioavailability due to various confounding factors, e.g. type of AED, dose of ER and DR, number of subjects on a particular AED etc.

The overall distribution for the AUC<sub>24</sub>, C<sub>max</sub> and C<sub>min</sub> is comparable for the Depakote ER and DR regimens for the entire population with the coadministration of various AEDs as shown in the following figures.





**Are the analytical methodologies for the assessment of valproic acid adequate?**

\_\_\_\_\_

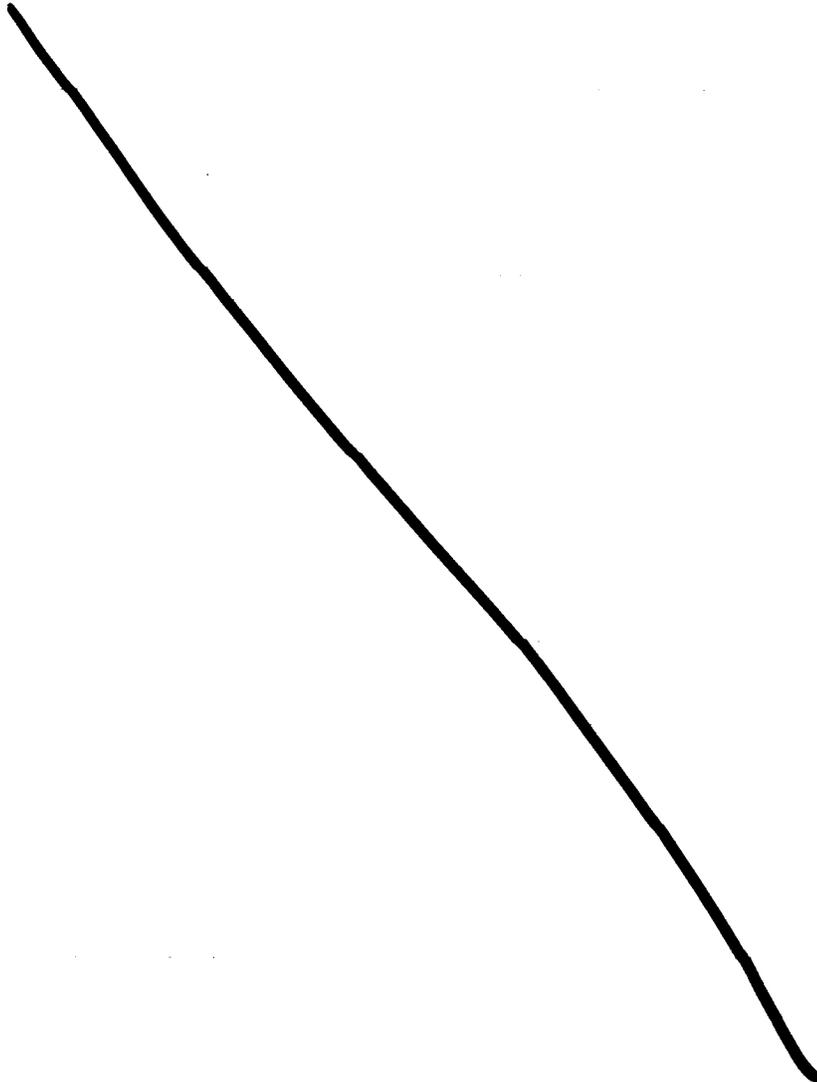
**Was the DSI inspection of Study M01-274 satisfactory?**

The DSI inspection results are expected by the end of November. The acceptability of the study results will depend on the DSI inspection results

### **LABELING RECOMMENDATION**

The following labeling changes in the "Pharmacokinetics" section under "CLINICAL PHARMACOLOGY" section of the label as shown by track changes should be conveyed to the sponsor and the Reviewer's Comment regarding the "DOSAGE AND ADMINISTRATION" section of the label should be conveyed to the Medical Officer:

#### **CLINICAL PHARMACOLOGY**



2 pages redacted from this section of the approval package  
consisted of draft labeling

***Comment to the Medical Officer:***

- 1. In the conversion Table 5, the BE study did not provide adequate number of subjects beyond an ER dose of 3500 mg. Only 4 subjects were enrolled at doses higher than 3500 mg. The conversion outlined in the Table beyond this dose should be made on a Clinical basis.*

*In addition to these high doses there are various interim doses (increments of 250 mg ER dose) that have not been evaluated directly, however, increments of 500 mg in the range from 1000-3500 mg has been evaluated with reasonable number of subjects in each dose group. Hence, the sponsor's proposal of adding dose increments of 250 mg up to 3500 mg ER dose in the Dose Conversion Table should be acceptable.*
- 2. Even though equivalence was shown between ER and DR (at AUC, C<sub>max</sub> and C<sub>min</sub>), the sponsor proposed the following statement "Plasma valproate C<sub>min</sub> concentrations for DEPAKOTE ER on average are equivalent to DEPAKOTE DELAYED-RELEASE TABLETS, but may vary across patients after conversion. . If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL) (see **Pharmacokinetics**-Absorption/Bioavailability)" When equivalence is demonstrated such a statement is unusual.*

## **APPENDIX**

### **INDIVIDUAL STUDY REVIEW**

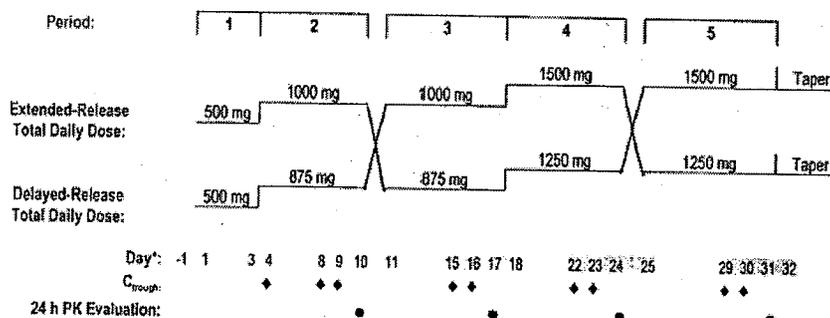
**Study M00-232:** *Comparison of the bioavailability of Depakote ER formulation (1000 and 1500 mg total daily dose) relative to Depakote DR formulation (875 and 1250 mg total daily dose) in healthy volunteers*

Objectives:

The primary objective of this study was a pharmacokinetic comparison of Depakote ER QD regimen to that of Depakote DR BID regimen, with larger daily doses for the ER regimen. The ratios for comparison were 8:7 and 6:5.

The study design is as follows:

|                  |  |
|------------------|--|
| Study Design     | Multiple dose, titration, fasting, open label, randomized, single center, 5-period crossover design  |
| Study Population | N=35 healthy subjects,<br>Gender:23M &12F [Sequence 1:15M &3F, Sequence 2: 8M&9F]<br>Age:19-55 yrs (mean 36 yrs),<br>Weight: 59.3-105.3 kg (mean 76.4 kg),<br>Race: 30 Caucasians, 4 Black, 1 Asian<br>Mean age, weight and race were similar for the two dose sequences |
| Treatment Group  | A1: Depakote ER 1000 mg QD,<br>A2: Depakote ER 1500 mg QD,<br>B1: Depakote DR 875 mg given as divided doses BID(500+375 mg),<br>B1: Depakote DR 1250 mg given as divided doses BID (625+625 mg),<br>5-Period, 2 sequence : Equal numbers in two sequence groups as below |



|                           |   |
|---------------------------|---|
|                           | Depakote ER: Lot 67-791-AA-21 for 500 mg<br>Depakote DR: Lot 65-533-AA-21 for 125 mg, 65-526-AA-21 for 250 mg, 67-709-AA-21 for 500 mg  |
| Dosage and Administration | 1000 mg ER given as: two 500 mg tablets at AM<br>1500 mg ER given as : three 500 mg tablets at AM<br><br>875 mg DR given as: one 500 mg tablets at AM and 250+125 mg tablets at PM<br>1250 mg DR given as: 500+125 mg tablet at AM and PM<br><br><u>Diet:</u><br>-Morning doses administered under fasting conditions |

|                 |   |              |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
|-----------------|---|--------------|---------------|--------------|----------------|------------|--------|-------------|------|------|------|------|------|-------------|------|------|------|------|------|
|                 | <p>-Evening doses under modified fasting conditions, i.e. fast approx 3.5 hrs before and 1 hr after evening dose</p> <table border="0"> <tr> <td>Regimen</td> <td>AM Dose</td> <td>Lunch</td> <td>Snack</td> <td>PM Dose</td> <td>Dinner</td> </tr> <tr> <td>Depakote ER</td> <td>0730</td> <td>1130</td> <td>1600</td> <td>None</td> <td>2030</td> </tr> <tr> <td>Depakote DR</td> <td>0730</td> <td>1130</td> <td>1600</td> <td>1930</td> <td>2030</td> </tr> </table> <p>Meal Content was identical on Extensive PK sampling Days, no grape fruit juice allowed.</p> <p>Subjects received drug from Day 1-36</p> <p>5 periods not separated by washout periods<br/>All subjects received all four regimens</p> | Regimen      | AM Dose       | Lunch        | Snack          | PM Dose    | Dinner | Depakote ER | 0730 | 1130 | 1600 | None | 2030 | Depakote DR | 0730 | 1130 | 1600 | 1930 | 2030 |
| Regimen         | AM Dose   | Lunch        | Snack         | PM Dose      | Dinner         |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Depakote ER     | 0730  | 1130         | 1600          | None         | 2030           |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Depakote DR     | 0730  | 1130         | 1600          | 1930         | 2030           |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Sampling: Blood | <p><u>Trough Concentrations on Days 1, 4, 8, 9, 15, 16, 22, 23, 29 and 30: 10 minutes prior to dosing (0 hr)</u><br/><u>PK Profile on Days 10, 17, 24 and 31: 10 minutes prior to dosing (0 hr) and 1.5, 3, 4.45, 6, 7.5, 9, 12, 13.5, 16.5, 19.5, 21 and 24 hours post dose</u></p>  |              |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Urine           | None  |              |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Feces           | None  |              |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Analysis        | <p><u>For Valproic acid:</u> [REDACTED]</p> <p><u>Lower Limits of Quantitation</u></p> <table border="0"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> <td style="text-align: center;"><u>Urine</u></td> </tr> <tr> <td>Valproic acid:</td> <td style="text-align: center;">[REDACTED]</td> <td style="text-align: center;">none</td> </tr> </table> <p>Accuracy and precision [REDACTED]</p>  |              | <u>Plasma</u> | <u>Urine</u> | Valproic acid: | [REDACTED] | none   |             |      |      |      |      |      |             |      |      |      |      |      |
|                 | <u>Plasma</u>   | <u>Urine</u> |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |
| Valproic acid:  | [REDACTED]  | none         |               |              |                |            |        |             |      |      |      |      |      |             |      |      |      |      |      |

Criteria for Evaluation:

*Pharmacokinetic Analysis:*

Parameters evaluated were AUC<sub>24</sub>, C<sub>max</sub>, C<sub>min</sub> and degree of fluctuation (DFL)  
[DFL=(C<sub>max</sub>-C<sub>min</sub>)/C<sub>avg</sub>; where C<sub>avg</sub>=AUC<sub>24</sub>/24]

*Statistical Analysis:*

The objective of this study was to show that the ER regimens were equivalent to the corresponding DR regimens with respect to AUC and equivalent or better than the corresponding DR regimens with respect to C<sub>max</sub> and C<sub>min</sub>.

ANOVA Tests

- Two one-sided tests procedure was performed for AUC.
- One-sided tests were performed to C<sub>max</sub> and C<sub>min</sub>

AUC and C<sub>max</sub> were log transformed and C<sub>min</sub> was not log transformed as the data showed that the logarithm of C<sub>min</sub> had a less symmetric probability distribution than the untransformed data. The effect of sequence, subject nested within sequence, period and regimen were evaluated. The effect of subject was random, all other effects were fixed.

*Acceptance Criteria*

- The range of acceptability for the ratio of the regimen central values should be 0.80-1.25 for AUC (90% CI)
- The ratio of the Depakote ER central value to that of Depakote DR central value for Cmin should be  $\geq 0.80$  (95% CI)
- The ratio of the Depakote ER central value to that of Depakote DR central value for Cmax should be  $\leq 1.25$  (95% CI)
- All these were tested at a significance level of 0.05

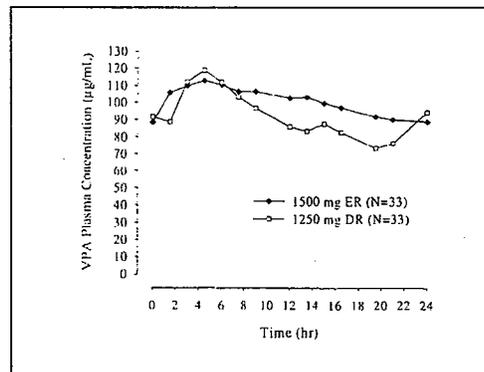
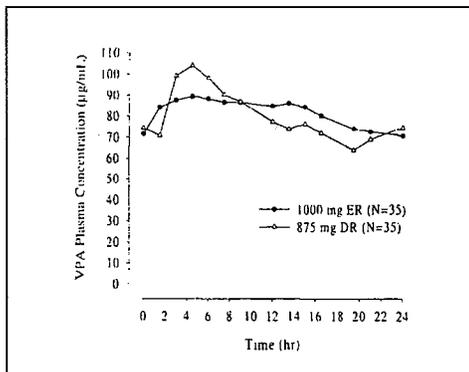
Pharmacokinetic Results:

The mean pharmacokinetic parameters  $\pm$  SD (%CV) are given in the following Table:

| PK Parameters  | Depakote Regimen             |                                  |                              |                                   |
|--|------------------------------|----------------------------------|------------------------------|-----------------------------------|
|  | 1000 mg ER<br>Test<br>(N=35) | 875 mg DR<br>Reference<br>(N=35) | 1500 mg ER<br>Test<br>(N=33) | 1250 mg DR<br>Reference<br>(N=33) |
| AUC <sub>24</sub> ( $\mu\text{g}\cdot\text{h}/\text{ml}$ ) | 1970 $\pm$ 402 (20)          | 1920 $\pm$ 355 (18)              | 2422 $\pm$ 397* (16)         | 2204 $\pm$ 345 (16)               |
| C <sub>max</sub> ( $\mu\text{g}/\text{ml}$ )               | 96.0 $\pm$ 18.5* (19)        | 112 $\pm$ 18.0 (16)              | 116 $\pm$ 17* (15)           | 127 $\pm$ 19.3 (15)               |
| C <sub>min</sub> ( $\mu\text{g}/\text{ml}$ )               | 65.4 $\pm$ 17.5 (27)         | 59.1 $\pm$ 12.9 (22)             | 82.2 $\pm$ 19.1* (23)        | 66.4 $\pm$ 14 (21)                |
| T <sub>max</sub> (h)                                       | 7.7 $\pm$ 5.3 (69)           | 4.0 $\pm$ 1.5 (36)               | 6.2 $\pm$ 4.1(66)            | 4.5 $\pm$ 2.7 (62)                |
| DFL  | 0.386 $\pm$ 0.146*<br>(38)   | 0.6790 $\pm$ 0.158<br>(24)       | 0.344 $\pm$ 0.150*<br>(44)   | 0.667 $\pm$ 0.171 (26)            |

\*Statistically significantly different than reference DR regimen (p<0.05)

The mean pharmacokinetic profiles for the 1000 mg ER/875 mg DR regimen and the 1500 mg ER /1250 mg DR regimen are shown in the following figures:



It is interesting to note that the mean Depakote DR BID regimen profile does not show two peaks.

This lack of or delay of the second peak after the second dose is quite likely due to the effect of evening meals based on the sponsor's discussions. The morning dose was given after a 10 hour fast, where as the evening dose was given under modified fasting conditions with dosing 3.5 hours after a light snack and dinner 1 hour after the evening dose. The DR dosage form is an enteric coated tablet that is designed to resist dissolution in the acidic gastric environment. Therefore dissolution and absorption of valproic acid

begins after the tablet is passed into the small intestine. It appears that for the DR tablet, due to dinner after the evening dose, gastric emptying is delayed and hence the release of the tablet to the small intestine. Under fasting conditions Tmax usually occurs after 3-6 hour post dose, but is delayed after the evening dose.

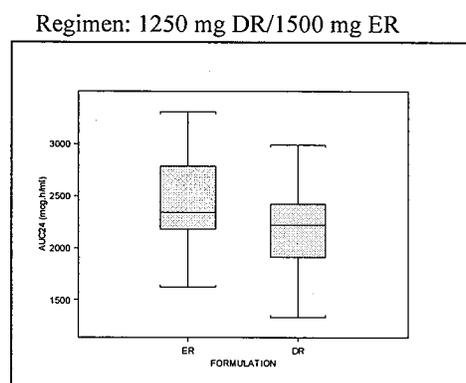
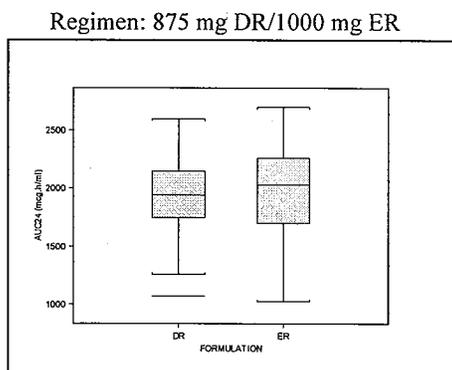
Looking at the individual plot it was observed that the evening Tmax was delayed in most subjects, but not all.

**Statistical Results:**

*Two one-sided test for AUC24:*

| Regimens<br>T vs R  | Parameter | Central Value*<br>Test (T) | Central Value*<br>Reference (R) | Point<br>Estimate** | 90% CI      |
|---|-----------|----------------------------|---------------------------------|---------------------|-------------|
| 1000 mg ER vs.<br>875 mg DR   | AUC24     | 1923                       | 1887                            | 1.019               | 0.966-1.075 |
| 1500 mg ER vs.<br>1250 mg DR  | AUC24     | 2393                       | 2170                            | 1.103               | 1.068-1.139 |
| * Antilogarithm of the least square means for logarithms                    |           |                            |                                 |                     |             |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                            |                                 |                     |             |

- Two one sided test based on log transformed AUC24 showed that the 1000 mg Depakote ER was equivalent to 875 mg Depakote DR, and 1500 mg Depakote ER was equivalent to 1250 mg Depakote DR with respect to AUC24, since the 90% CI were within the 0.80-1.25 range.
- The box plots showing the distribution of AUC24 for the two sequences are shown below



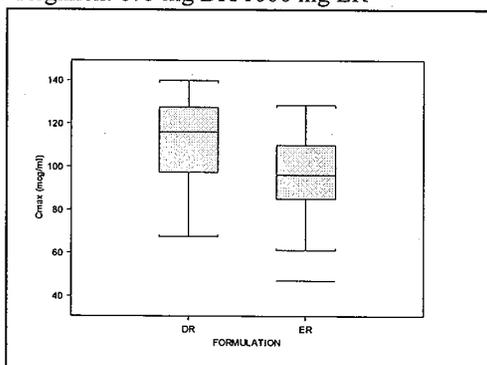
- The AUC24 for the 875/1000 regimen are very comparable, however, the 1500 mg ER have 10% higher AUC than the 1250 mg DR regimen, although they are within the 90% CI.

*One-sided test for Cmax:*

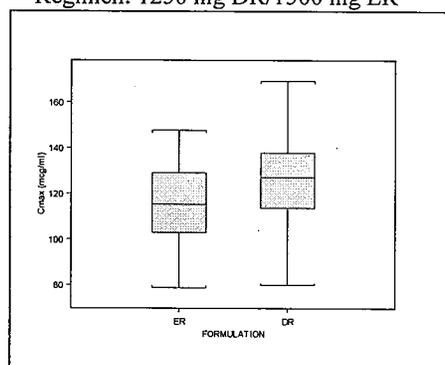
| Regimens<br>T vs R  | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference<br>(R) | Point<br>Estimate** | Upper 95%<br>confidence<br>bound | 90% CI      |
|---|-----------|-------------------------------|---------------------------------------|---------------------|----------------------------------|-------------|
| 1000 mg ER vs.<br>875 mg DR   | Cmax      | 94.01                         | 110.2                                 | 0.853               | 0.892                            | 0.814-0.892 |
| 1500 mg ER vs.<br>1250 mg DR  | Cmax      | 114.6                         | 125.3                                 | 0.914               | 0.939                            | 0.889-0.939 |
| * Antilogarithm of the least square means for logarithms                    |           |                               |                                       |                     |                                  |             |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                               |                                       |                     |                                  |             |

- The ER regimen is acceptable for Cmax based on the protocol specified criteria, as the analysis for the log-transformed Cmax showed that the 95% upper confidence bound for the ratio of the regimen Cmax central values were lower than 1.25
- The 90% CI calculated by the reviewer were also within the acceptable limits.
- The box plots showing the distribution of Cmax for the two sequences are shown below:

Regimen: 875 mg DR/1000 mg ER



Regimen: 1250 mg DR/1500 mg ER



- In both regimens the ER has lower Cmax, as compared to the DR.

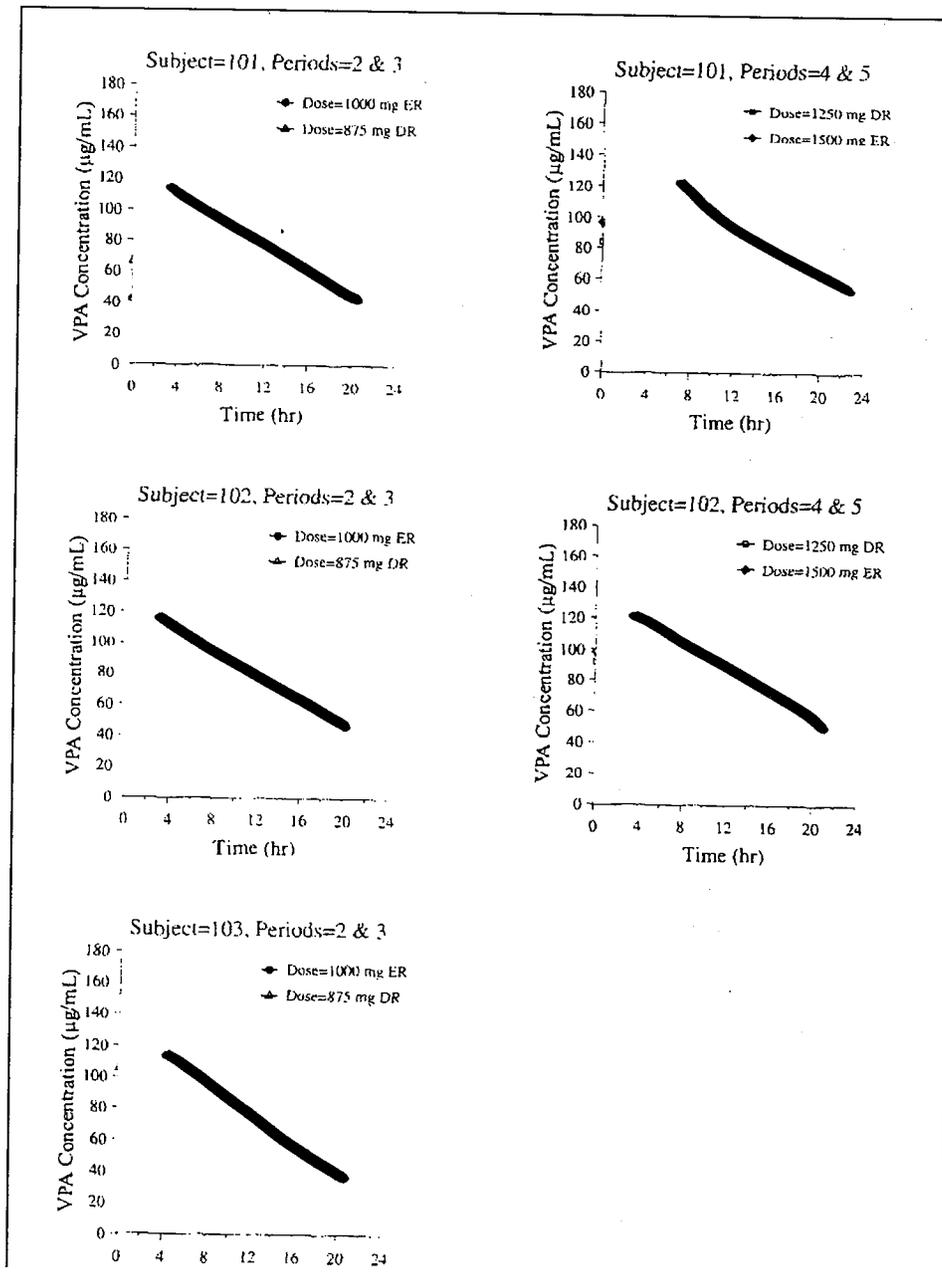
*One-sided test for Cmin:*

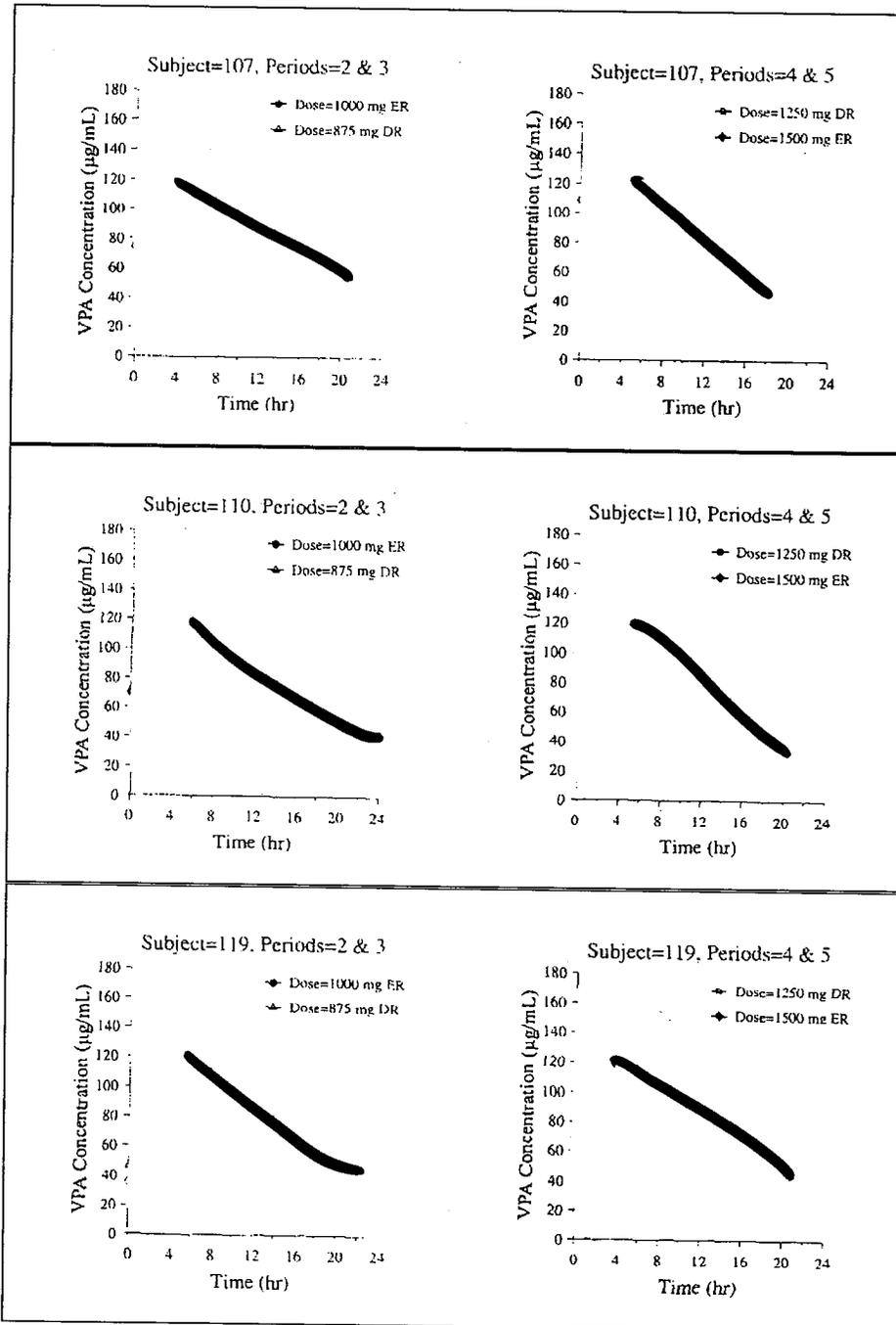
| Regimens<br>T vs R                      | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference<br>(R) | Point<br>Estimate*   | Lower 95%<br>confidence<br>bound | 90% CI      |
|---|-----------|-------------------------------|---------------------------------------|----------------------|----------------------------------|-------------|
| 1000 mg ER vs.<br>875 mg DR             | Cmin      | 65.32                         | 59.11                                 | 1.105<br>(0.53-1.96) | 1.014                            | 0.997-1.198 |
| 1500 mg ER vs.<br>1250 mg DR            | Cmin      | 82.37                         | 66.11                                 | 1.246<br>(0.71-1.86) | 1.164                            | 1.157-1.330 |
| * Ratio (T/R) of the least square means |           |                               |                                       |                      |                                  |             |

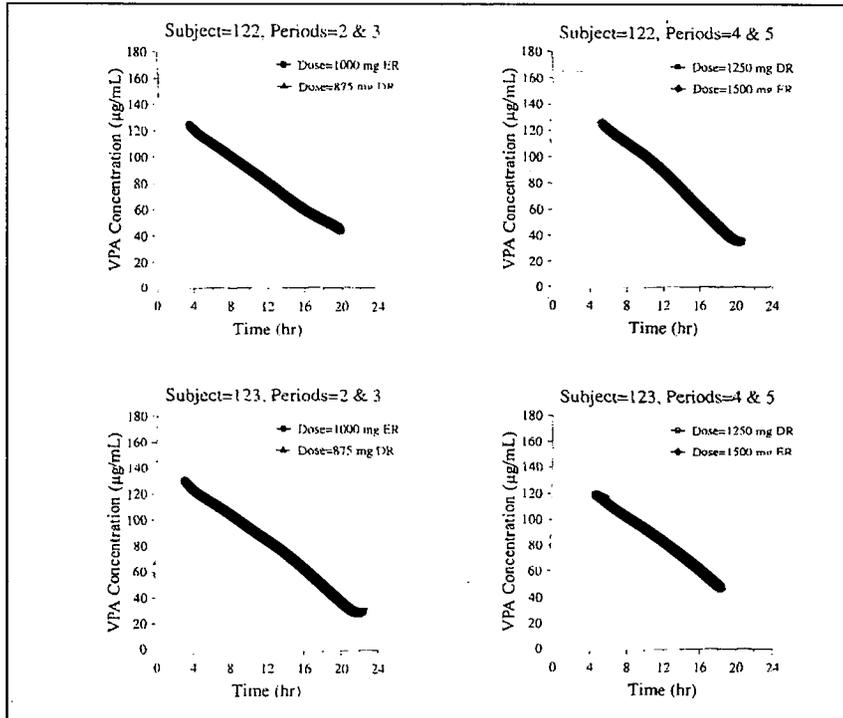
- The ER regimen is acceptable for Cmin based on the protocol specified criteria, as the analysis for the Cmin showed that the 95% upper confidence bound for the ratio of the regimen Cmin central values were greater than 0.80
- The 90% CI on log transformed Cmin as calculated by the reviewer were within the acceptable limits for the 1000 mg ER/875 mg DR regimen, but was outside the upper

limit for 1500 mg ER/1250 mg DR regimen. As long as the Cmin is higher for the ER regimen, compared to the DR regimen, it is not likely to be a concern for reduced efficacy from the ER formulation.

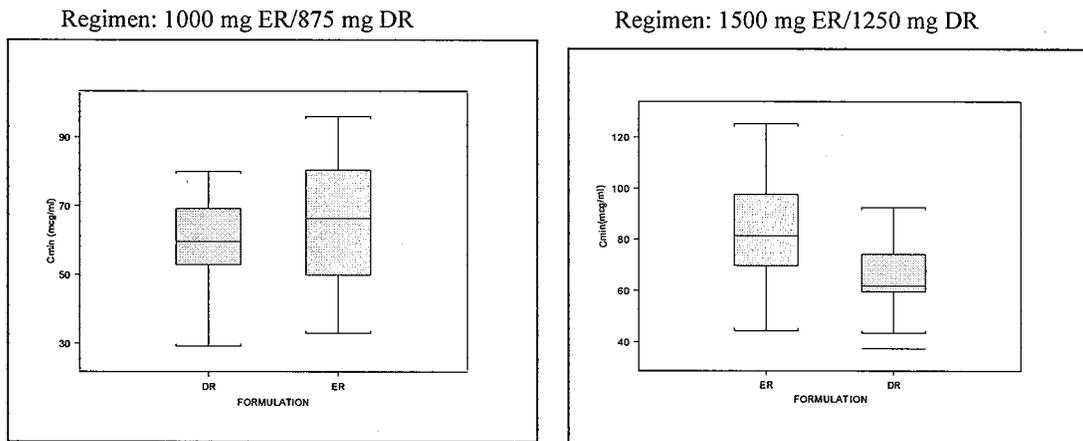
- Looking at individual values for 1000 mg ER/875 mg, it was observed that 7 out of 35 subjects had Cmin ratios lower than 0.8. The ratios were 0.62 (#101), 0.70 (#102), 0.53 (#103), 0.60 (#110), 0.79 (#119), 0.74 (#122) and 0.72 (#123). For 1500 mg ER/1250 mg DR regimen, only 2 subjects has Cmin ratios lower than 0.8, values being 0.71 (#107) and 0.74 (#110). Looking at the 24 hour profile of these subjects it was observed that the ER regimen has lower concentrations at all time points (See figures below). Although, the Cmin ratios were lower in these subjects, the individual Cmin values were comparable to the distribution of the Cmin values in the entire population, as shown in the Box plot in the following pages. Subject 110 was the only subject that showed a lower Cmin value of the ER formulation at both dosing regimens (1000 and 1500 mg ER). The others could be attributed to the population variability.







- The box plots showing the distribution of Cmax for the two sequences is shown in the following figures:



- The mean Cmin for the ER regimen is higher than the DR regimen. For the 1500 mg ER regimen, the mean Cmin is 25% higher as compared to the DR regimen. The lowest Cmin in the ER population is comparable to the DR regimen

Relative Bioavailability:

- The estimates of relative bioavailability of 1000 mg ER compared to 875 mg DR regimen was [REDACTED]
- The estimates of relative bioavailability of 1500 mg ER compared to 1250 mg DR regimen was [REDACTED]

Overall Conclusions:

- In healthy volunteers for 1000 mg ER/875 mg DR and 1500 mg ER/1250 mg DR comparisons, equivalence was established between ER and DR for AUC, C<sub>max</sub> and C<sub>min</sub>. Depakote ER DFL was lower than Depakote DR DFL.

**APPEARS THIS WAY ON ORIGINAL**

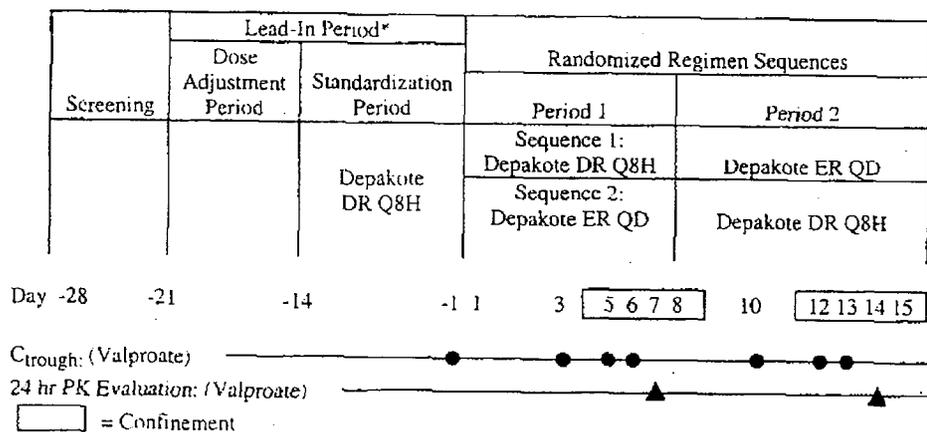
**Study M01-274:** *Comparison of the bioavailability of Depakote ER formulation relative to Depakote DR formulation in adult patients with epilepsy on the Depakote DR formulation and an enzyme inducing antiepileptic drug.*

Objectives:

The primary objective of this study was to compare the pharmacokinetics of Depakote ER formulation given QD relative to the DR formulation given Q8H using various Depakote ER doses that are 8-20% greater than the corresponding DR total daily doses in patients with epilepsy currently receiving Depakote DR and an enzyme inducing antiepileptic drug (AED), such as carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone or topiramate.

The study design is as follows:

|                  |  |
|------------------|--|
| Study Design     | Multiple dose, modified fasting, open label, randomized, multi-center, 2-period crossover design   |
| Study Population | N=64 epilepsy patients on Depakote DR and any of the enzyme inducing AEDs<br><u>Gender:</u> 30M & 34F<br><u>Age:</u> 18-73 yrs (mean 40 yrs),<br><u>Weight:</u> 51.7-139 kg (mean 87.6 kg),<br><u>Race:</u> 56 Caucasians, 8 Black |
| Treatment Group  | A: Depakote ER QD,<br>B: Depakote DR Q8H<br>Each subject received both regimens.<br>Period 1: Day 1-7, Regimen AB<br>Period 2: Day 8-14, Regimen BA<br><br>No washout interval between two study period                            |



\* Dose adjustment, if needed, occurred during the first 7 days (dose adjustment period). Once dose adjustments were completed, subjects received the same total daily Depakote DR doses Q8H for the last 14 consecutive days (standardization lead in period). If less than 7 days were needed to adjust the doses, the 14-day standardization period could have begun early.

|                           | <p>Depakote ER: Lot 66-661-AA-21 for 500 mg<br/>                 Depakote DR: Lot 73-405-AA-22 for 125 mg, 73-370-AA-21 for 250 mg, 72-366-AA-21 for 500 mg</p>  |         |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
|---------------------------|--|---------|-------------|-------|----------------|---------|--------|---------|-------------|------|------|------|------|------|------|-------------|------|------|------|------|------|------|
| Dosage and Administration | <p>Depakote ER total daily dose was 8-20% higher than the Depakote DR dose. Each dose was taken orally with 240 ml water, doses administered is given in the results section. DR doses ranged from 875 mg-4250 mg, however, fewer subjects were recruited at doses greater than 3500 mg.</p> <p>Subjects received drug (ER and DR) from Day 1-7 and 8-14 in a crossover manner</p> <p>All subjects received all regimens</p> <p>Concomitant AEDs administered to all subjects.</p> <p><u>Diet:</u><br/>                 -Morning doses administered after a 10 hr fast and 4 hrs fasting post dose<br/>                 -Midday and Evening doses in between meals as shown below</p> <p>Meal Schedule relative to Day 7 and 14:</p> <table border="1"> <thead> <tr> <th>Regimen</th> <th>AM Dose</th> <th>Lunch</th> <th>Midday Dose</th> <th>Snack</th> <th>Dinner</th> <th>PM Dose</th> </tr> </thead> <tbody> <tr> <td>Depakote ER</td> <td>0730</td> <td>1130</td> <td>None</td> <td>1700</td> <td>2100</td> <td>None</td> </tr> <tr> <td>Depakote DR</td> <td>0730</td> <td>1130</td> <td>1530</td> <td>1700</td> <td>2100</td> <td>2330</td> </tr> </tbody> </table> <p>Meal Content was identical on Extensive PK sampling Days, no grape fruit juice allowed.</p> | Regimen | AM Dose     | Lunch | Midday Dose    | Snack   | Dinner | PM Dose | Depakote ER | 0730 | 1130 | None | 1700 | 2100 | None | Depakote DR | 0730 | 1130 | 1530 | 1700 | 2100 | 2330 |
| Regimen                   | AM Dose  | Lunch   | Midday Dose | Snack | Dinner         | PM Dose |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Depakote ER               | 0730   | 1130    | None        | 1700  | 2100           | None    |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Depakote DR               | 0730   | 1130    | 1530        | 1700  | 2100           | 2330    |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Sampling: Blood           | <p><u>Trough Concentrations on Days -1, 3, 5, 6, 10, 12, and 13:</u> 10 minutes prior to dosing (0 hr) on Study</p> <p><u>PK Profile for VPA on Days 7 and 14:</u> 10 minutes prior to dosing (0 hr) and 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 14, 16, 18, 19, 20, 22 and 24 hours post morning dose</p> <p><u>AED Concentrations on Day -1:</u> one sample will be taken for AED concentration assay only for verifying compliance</p>   |         |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Urine                     | None   |         |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Feces                     | None   |         |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Analysis                  | <p><u>For Valproic acid (VPA):</u> _____</p> <p>_____ as internal standard</p> <p><u>Lower Limits of Quantitation</u></p> <table border="1"> <thead> <tr> <th></th> <th>Plasma</th> <th>Urine</th> </tr> </thead> <tbody> <tr> <td>Valproic acid:</td> <td>_____</td> <td>none</td> </tr> </tbody> </table> <p>Accuracy and Precision _____</p>  |         | Plasma      | Urine | Valproic acid: | _____   | none   |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
|                           | Plasma   | Urine   |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |
| Valproic acid:            | _____  | none    |             |       |                |         |        |         |             |      |      |      |      |      |      |             |      |      |      |      |      |      |

Criteria for Evaluation:

*Pharmacokinetic Analysis:*

Parameters evaluated were AUC<sub>24</sub>, C<sub>max</sub>, C<sub>min</sub> and degree of fluctuation (DFL)  
 [DFL=(C<sub>max</sub>-C<sub>min</sub>)/C<sub>avg</sub>; where C<sub>avg</sub>=AUC<sub>24</sub>/24]

*Statistical Analysis:*

The objective of this study was to show that the ER regimens were equivalent to the corresponding DR regimens with respect to AUC and equivalent or better than the corresponding DR regimens with respect to C<sub>max</sub> and C<sub>min</sub>.

In the statistical analysis, the study subjects were viewed as a single sample and were not classified by Depakote dose level.

ANOVA Tests

- Two one-sided tests procedure was performed for AUC.
- One-sided tests were performed for C<sub>max</sub> and C<sub>min</sub>

AUC and C<sub>max</sub> were log transformed and C<sub>min</sub> was not log transformed. The effect of sequence, subject nested within sequence, period and regimen were evaluated. The effect of subject was random, all other effects were fixed. For variable for which logarithm transformation was used, the ratio of central values was defined as the exponentiation of the difference of the logarithm means. If no transformation was employed, the ratio of central values was the ratio of means.

*Acceptance Criteria*

- The range of acceptability for the ratio of the regimen central values should be 0.80-1.25 for AUC
- The ratio of the Depakote ER central value to that of Depakote DR central value for C<sub>min</sub> should be  $\geq 0.80$
- The ratio of the Depakote ER central value to that of Depakote DR central value for C<sub>max</sub> should be  $\leq 1.25$
- All these were tested at a significance level of 0.05

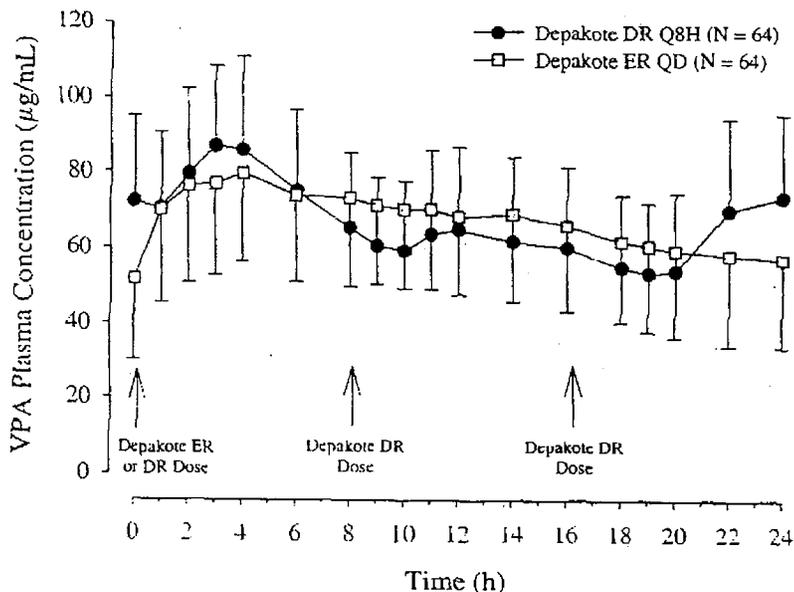
*Additional analysis performed:*

- To explore whether the bioavailability of the Depakote ER regimen relative to that of Depakote DR Q8H depends on the Depakote dose: this was based on regression analysis of the logarithm of the ratio of dose-normalized ER AUC<sub>24</sub> to DR AUC<sub>24</sub> values. Effects of sequence and total daily doses were included.
- To explore whether the relative bioavailability depends on the other AED the subject is taking. The test of primary interest was the test for the interaction of regimen and other AED.

Pharmacokinetic Results:

A total of 72 subjects were enrolled, 64 subjects had the PK analysis and 8 sample tubes broke during shipment.

The mean (SD) valproic acid plasma concentration time profile (N=64) is shown in the following figure:



The mean (SD) pharmacokinetic parameters for VPA at each dose level is given in the following Table:

| Depakote<br>Total Daily Dose | N  | Pharmacokinetic Parameters     |                             |                             |                         |                  |
|------------------------------|----|--------------------------------|-----------------------------|-----------------------------|-------------------------|------------------|
|                              |    | AUC <sub>24</sub><br>(µg·h/mL) | C <sub>max</sub><br>(µg/mL) | C <sub>min</sub><br>(µg/mL) | T <sub>max</sub><br>(h) | DFL              |
| DR Formulation               | 64 | 1600.6<br>(431.2)              | 96.1<br>(24.8)              | 44.9<br>(15.8)              | 6.5<br>(6.6)            | 0.790<br>(0.232) |
| ER Formulation               | 64 | 1630.5<br>(507.5)              | 86.8<br>(24.4)              | 45.9<br>(20.1)              | 7.1<br>(5.9)            | 0.641<br>(0.270) |
| 875 mg DR                    | 10 | 1080.2<br>(174.5)              | 66.4<br>(13.0)              | 28.8<br>(6.17)              | 5.8<br>(6.7)            | 0.841<br>(0.213) |
| 1000 mg ER                   | 10 | 1248.8<br>(369.8)              | 64.0<br>(18.6)              | 37.7<br>(13.6)              | 10.4<br>(8.5)           | 0.524<br>(0.172) |
| 1250 mg DR                   | 11 | 1383.4<br>(311.4)              | 80.7<br>(15.1)              | 38.4<br>(11.9)              | 5.2<br>(6.2)            | 0.768<br>(0.231) |
| 1500 mg ER                   | 11 | 1371.6<br>(422.1)              | 77.7<br>(23.5)              | 39.2<br>(17.1)              | 6.6<br>(4.4)            | 0.733<br>(0.400) |

| Depakote<br>Total Daily Dose | N  | Pharmacokinetic Parameters                                    |   |   |                         | DFL               |
|------------------------------|----|---|---|---|-------------------------|-------------------|
|                              |    | AUC <sub>24</sub><br>( $\mu\text{g}\cdot\text{h}/\text{mL}$ ) | C <sub>max</sub><br>( $\mu\text{g}/\text{mL}$ ) | C <sub>min</sub><br>( $\mu\text{g}/\text{mL}$ ) | T <sub>max</sub><br>(h) |                   |
| 1375 mg DR                   | 4  | 1498.2<br>(241.2)   | 96.8<br>(14.4)                                  | 41.3<br>(10.8)                                  | 2.8<br>(1.0)            | 0.905<br>(0.325)  |
| 1500 mg ER                   | 4  | 1284.0<br>(138.0)   | 77.4<br>(10.2)                                  | 32.1<br>(2.83)                                  | 4.0<br>(3.7)            | 0.838<br>(0.118)  |
| 1750 mg DR                   | 16 | 1635.4<br>(329.0)   | 98.8<br>(22.1)                                  | 47.7<br>(12.1)                                  | 7.2<br>(6.9)            | 0.762<br>(0.215)  |
| 2000 mg ER                   | 16 | 1608.0<br>(429.8)   | 85.4<br>(22.4)                                  | 45.2<br>(19.8)                                  | 5.6<br>(5.0)            | 0.628<br>(0.197)  |
| 2125 mg DR                   | 3  | 2141.8<br>(224.1)   | 127<br>(6.55)                                   | 63.3<br>(15.8)                                  | 3.7<br>(0.6)            | 0.721<br>(0.181)  |
| 2500 mg ER                   | 3  | 2147.6<br>(304.2)   | 106<br>(14.5)                                   | 62.5<br>(16.5)                                  | 7.7<br>(7.2)            | 0.503<br>(0.183)  |
| 2250 mg DR                   | 4  | 1972.2<br>(187.2)   | 111<br>(10.7)                                   | 58.6<br>(4.58)                                  | 8.8<br>(8.9)            | 0.633<br>(0.0446) |
| 2500 mg ER                   | 4  | 2306.9<br>(331.7)   | 116<br>(16.7)                                   | 71.8<br>(7.1)                                   | 7.8<br>(5.9)            | 0.456<br>(0.106)  |
| 2500 mg DR                   | 4  | 1923.2<br>(516.6)   | 108<br>(29.3)                                   | 56.9<br>(18.2)                                  | 10.3<br>(8.5)           | 0.638<br>(0.0364) |
| 3000 mg ER                   | 4  | 2187.0<br>(497.1)   | 105<br>(20.2)                                   | 63.5<br>(26.3)                                  | 8.5<br>(6.4)            | 0.481<br>(0.170)  |
| 3000 mg DR                   | 8  | 1742.7<br>(130.6)   | 109<br>(14.2)                                   | 43.3<br>(11.4)                                  | 6.0<br>(8.2)            | 0.914<br>(0.307)  |
| 3500 mg ER                   | 8  | 1745.3<br>(202.2)   | 92.0<br>(11.0)                                  | 45.7<br>(20.2)                                  | 6.9<br>(4.0)            | 0.657<br>(0.252)  |
| 3500 mg DR                   | 1  | 3063.0<br>NA  | 163<br>NA                                       | 101<br>NA                                       | 11.0<br>NA              | 0.482<br>NA       |
| 4000 mg ER                   | 1  | 2993.7<br>NA  | 146<br>NA                                       | 82.9<br>NA                                      | 22.0<br>NA              | 0.504<br>NA       |
| 4000 mg DR                   | 2  | 1815.1<br>(145.2)   | 112<br>(6.33)                                   | 49.7<br>(11.2)                                  | 13.5<br>(3.5)           | 0.824<br>(0.130)  |
| 4500 mg ER                   | 2  | 1668.4<br>(370.3)   | 110<br>(17.8)                                   | 43.3<br>(17.1)                                  | 2.5<br>(0.7)            | 0.979<br>(0.207)  |
| 4250 mg DR                   | 1  | 1618.6<br>NA  | 122<br>NA                                       | 40.3<br>NA                                      | 3.0<br>NA               | 1.20<br>NA        |
| 5000 mg ER                   | 1  | 1201.2<br>NA  | 81.3<br>NA                                      | 14.6<br>NA                                      | 4.0<br>NA               | 1.33<br>NA        |

NA Not applicable

- Looking at these mean values it can be observed that mean C<sub>max</sub> was mostly lower for the ER regimen as compared to the DR regimen for most doses.
- The mean C<sub>min</sub> was comparable or higher for most doses of ER as compared to the DR, except for 1500 mg ER/1375 mg DR, 4000 mg ER/3500 mg DR and 4500 mg ER/4000 mg DR, 5000 mg ER/4500 mg DR regimen, where the C<sub>min</sub> of ER regimen

was lower than the DR regimen. However, these dose groups had fewer subjects (1-4 in total).

- Mean DFL was lower for ER regimen at all doses.
- The test statistic for period effects was only significant for Cmax (p=0.0455) and not for the other parameters for the ER and DR comparisons.
- Total Variability (%CV) in the PK parameters is given below:

| Parameter | Depakote DR Q8H (n=64) | Depakote ER QD (n=64) |
|-----------|------------------------|-----------------------|
| AUC       | 27                     | 31                    |
| Cmax      | 26                     | 28                    |
| Cmin      | 35                     | 44                    |

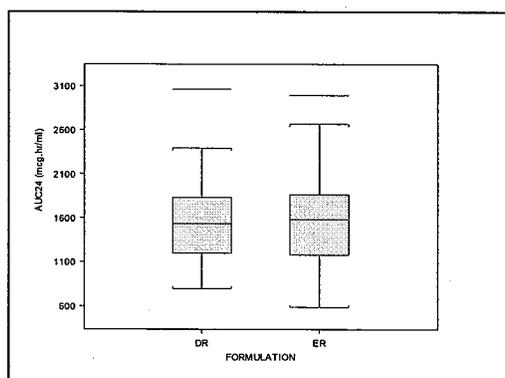
Statistical Results:

*Two one-sided test for AUC24:*

| Regimens<br>T vs R  | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference (R) | Point<br>Estimate**           | 90% CI      | p-value |
|---|-----------|-------------------------------|------------------------------------|-------------------------------|-------------|---------|
| ER QD vs.<br>DR Q8H   | AUC24     | 1551                          | 1539                               | 1.008<br>range<br>(0.87-1.05) | 0.964-1.055 | 0.7575  |
| * Antilogarithm of the least square means for logarithms                    |           |                               |                                    |                               |             |         |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                               |                                    |                               |             |         |

- Two one sided test based on log transformed AUC24 showed that the Depakote ER QD was equivalent to Depakote DR Q8H with respect to AUC24, since the 90% CI were within the 0.80-1.25 range.
- The box plots showing the distribution of AUC24 for the two formulations is shown below:

Regimen: DR Q8H/ ER QD



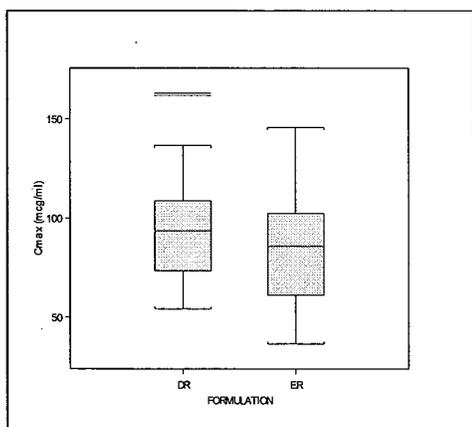
- The DR and ER regimen have an overlapping range of AUC24 values.

*One-sided test for Cmax:*

| Regimens<br>T vs R  | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference (R) | Point<br>Estimate**           | Upper<br>95%<br>confidence<br>bound<br>(log trans) | 90% CI<br>(log-<br>trans) | p-value |
|---|-----------|-------------------------------|------------------------------------|-------------------------------|--|---------------------------|---------|
| ER QD vs.<br>DR Q8H   | Cmax      | 83.27                         | 92.59                              | 0.899<br>range<br>(0.82-1.09) | 0.938  | 0.864-<br>0.938           | 0.0001  |
| * Antilogarithm of the least square means for logarithms                    |           |                               |                                    |                               |  |                           |         |
| ** Antilogarithms of the difference of the least square mean for logarithms |           |                               |                                    |                               |  |                           |         |

- The ER regimen is acceptable for Cmax, as the analysis for the log transformed Cmax showed that the 95% upper confidence bound for the ratio of the regimen Cmax central values were 0.899, which is lower than 1.25
- The 90% CI on log transformed data calculated by the reviewer were also within the acceptable limits (0.86-0.93) as well.
- The box plots showing the distribution of Cmax for the two regimens are shown below:

Regimen: DR Q8H/ ER QD



- The ER regimen has a lower range of Cmax values, as compared to the DR regimen.

*One-sided test for Cmin:*

| Regimens<br>T vs R                       | Parameter | Central<br>Value*<br>Test (T) | Central<br>Value*<br>Reference (R) | Point<br>Estimate**           | Lower 95%<br>confidence<br>bound<br>(untrans) | 90% CI<br>(log trans) | p-value |
|--|-----------|-------------------------------|------------------------------------|-------------------------------|---|-----------------------|---------|
| ER QD vs.<br>DR Q8H                      | Cmin      | 45.85<br>range<br>(20.1-98.2) | 44.82<br>range<br>(15.5-101.4)     | 1.022<br>range<br>(0.28-2.40) | 0.950   | 0.888-1.06            | 0.6149  |
| ** Ratio (T/R) of the least square means |           |                               |                                    |                               |   |                       |         |

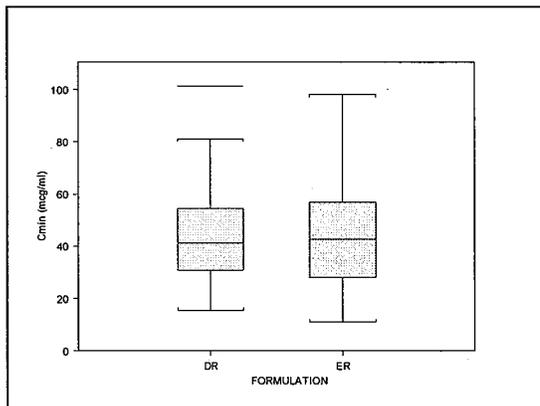
- The parameter Cmin was not log transformed by the sponsor as the data showed that the logarithm of Cmin had a less symmetric probability distribution than the untransformed data.
- The ER regimen is acceptable for Cmin, as the analysis for the Cmin showed that the 95% lower confidence bound for the ratio of the regimen Cmin central value was 0.95, which is greater than 0.80, as specified in the protocol.
- The mean Cmin for the ER was not statistically significantly different from the mean Cmin of the DR product.
- The 90% CI on log transformed Cmin as calculated by the reviewer were within the acceptable limits (0.88-1.06) for Cmin
- On Discussions with Dr. Don Schuirmann, Division of Biometrics, it was found that the sponsor's method for calculating 90% CI on untransformed data is not acceptable and methodology of LOCKE based on Fieller's theorem should be used. The program was provided by Dr. Schuirmann and was run by the reviewer. The 90% CI based on this method was 0.95-1.09 and was within the acceptable limits for BE testing. Thus equivalency in terms of Cmin was established based on all three statistical criteria, as shown in the following Table.

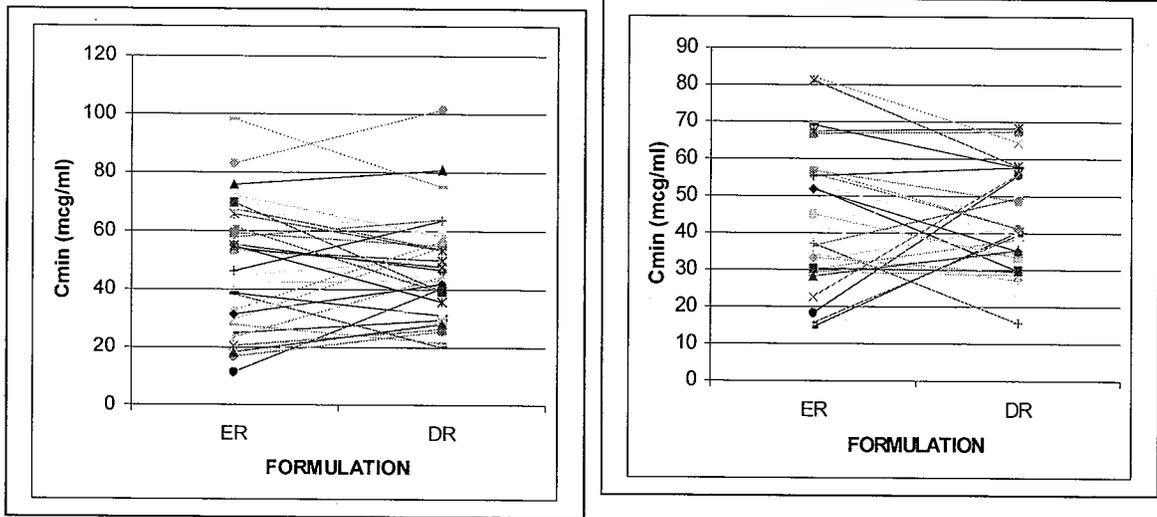
Statistical Tests for Cmin:

| Statistical Criteria  | Confidence bound or Confidence Interval |
|---|---|
| One-Sided Test (Untransformed Data)<br>Lower 95% Confidence bound | 0.95                                    |
| Two-sided Test (Log-transformed Data)<br>90% Confidence Interval  | 0.88-1.06                               |
| LOCKE'S Method (Untransformed Data)<br>90% Confidence Interval    | 0.95-1.09                               |

- The box plots showing the distribution of Cmin for the two regimen is shown in the following figure and the Stick plots show the individual differences in Cmin:

Regimen: DR Q8H/ ER QD





- Looking at individual data it was observed that six subjects had more than 2-fold lower Cmin for the ER regimen as compared to the DR regimen and 14 subjects (excluding the 6) had > 20% lower Cmin in the ER regimen as compared to the corresponding DR regimen. The low Cmin subjects did not belong to any particular dose group or to any particular group of patients taking the same concomitant AEDs. Although, some subjects have lower Cmin values for the ER formulation, they were within the population distribution of the Cmin values for Reference or Test, as shown by the distribution in Cmin values in the box plot. If adequate clinical response is not obtained, it would be desirable to monitor plasma valproate levels.

Steady State Attainment

Steady state was reached by Day 4 as Day 5, 6, and 7 trough concentrations were not statistically significantly different ( $p=0.1342$ ; Day 5 vs. Day 7)

Relative Bioavailability:

- The estimates of relative bioavailability of ER compared to DR regimen was 0.873
- The ER/DR ratio of dose normalized Cmax central values was estimated to be 0.779
- The ER/DR ratio of dose normalized Cmin central values was estimated to be 0.913

Effect of Depakote DR dose on the Depakote ER/DR relative bioavailability:

The total daily Depakote DR frequency is shown in the following Table:

| Dose (mg) | Frequency | Percent |
|-----------|-----------|---------|
| 875       | 10        | 15.6    |
| 1250      | 11        | 17.2    |
| 1375      | 4         | 6.3     |
| 1750      | 15        | 23.4    |
| 2000      | 1         | 1.6     |

|      |   |      |
|------|---|------|
| 2125 | 3 | 4.7  |
| 2250 | 4 | 6.3  |
| 2500 | 4 | 6.3  |
| 3000 | 8 | 12.5 |
| 3500 | 1 | 1.6  |
| 4000 | 2 | 3.1  |
| 4250 | 1 | 1.6  |

To investigate whether the bioavailability of the Depakote ER formulation relative to that of the Depakote DR Q8H changed with the Depakote DR dose, two approaches were taken by the sponsor:

1. A regression analysis was conducted on the ratio of dose normalized ER AUC<sub>24</sub> to DR AUC<sub>24</sub> values. The regression model included effects for sequence and total daily DR dose. The results showed that the bioavailability of Depakote ER relative to Depakote DR was independent of the total daily Depakote DR dose (p= 0.3041)
2. An analysis was conducted on the natural logarithm of dose normalized AUC<sub>24</sub> using an ANOVA after collapsing the total daily DR dose groups in the study into several larger dose groups. The dose groups were:
  - vi) Low: 875 mg DR; N=10
  - vii) Low intermediate: 1250-1375 mg DR; N=15
  - viii) Intermediate: 1750 mg DR; N=15
  - ix) High intermediate: 2000-2500 mg DR; N=12
  - x) High: 3000-4250 mg DR, N=12

The ANOVA model had fixed effects for sequence, dose group, the interaction between sequence and dose group, regimen, period, the interaction between dose group and regimen, a random effect for subject nested within the sequence and dose group combination.

The ER/DR relative bioavailability as given by the point estimate and the p-value is given in the following Table

| Parameter                       | Point Estimate<br>ER/DR Relative<br>Bioavailability | p-value |
|---------------------------------|---|---------|
| ER/DR: 875 mg dose group; N=10  | 0.99  | 0.8193  |
| ER/DR: 1250 mg dose group; N=15 | 0.80  | 0.0001  |
| ER/DR: 1750 mg dose group; N=15 | 0.84  | 0.0016  |
| ER/DR: 2250 mg dose group; N=12 | 0.96  | 0.5368  |
| ER/DR: 3500 mg dose group; N=12 | 0.85  | 0.0094  |
| ER/DR: Linear trend             |   | 0.5764  |
| ER/DR: 3500 vs 875 mg           |   | 0.1010  |

- The primary test for dose group and regimen interaction was not statistically significant (p=0.0645)
- A secondary test comparing the ER/DR relative bioavailability between the lowest (875 mg) and highest (3000 mg) DR dose groups was also not statistically significant (p=0.1010).

- A test for linear trend with Depakote DR dose on the ER/DR relative bioavailability was also not statistically significant ( $p=0.5764$ )
- The least square mean point estimates of ER/DR relative bioavailability of dose normalized AUC ratios for the different Depakote DR dose groups were 0.99, 0.80, 0.84, 0.96 and 0.85 for above 5 dose groups respectively.
- Looking at individual Cmins no trend was observed between dose group and low Cmins for the ER regimen.

Effect of enzyme-inducing AED on Depakote ER/DR relative bioavailability:

Concomitant AED are known to induce hepatic microsomal enzymes and may reduce systemic bioavailability of valproate.

The concomitant enzyme-inducing AEDs, their dose, concentration and frequency are given in the following Table. The AED concentrations were measured to ensure compliance, hence, do not necessarily represent trough concentrations.

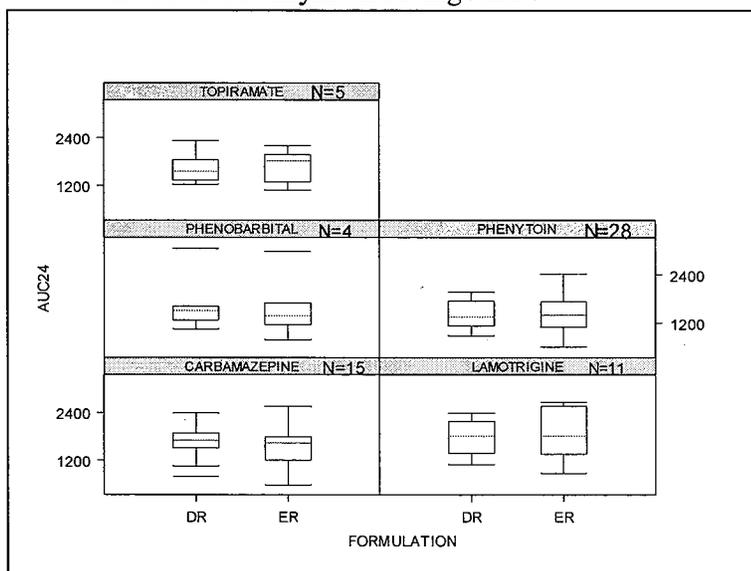
| AED           | Point Estimate | p-value | Dose (mg/day) |      | AED Concentration (µg/ml) |     | Frequency | Percent |
|---------------|----------------|---------|---------------|------|---------------------------|-----|-----------|---------|
|               |                |         | Min           | Max  | Min                       | Max |           |         |
| Carbamazepine | 0.79           | 0.0001  | 200           | 1500 |                           |     | 15        | 23.4    |
| Lamotrigine   | 0.93           | 0.2432  | 50            | 400  |                           |     | 11        | 17.2    |
| Phenobarbital | 0.87           | 0.1493  | 120           | 250  |                           |     | 4         | 6.3     |
| Phenytoin     | 0.89           | 0.0047  | 150           | 600  |                           |     | 28        | 43.8    |
| Primidone     |                |         | 1000          | 1000 |                           |     | 1         | 1.6     |
| Topiramate    | 0.96           | 0.6782  | 100           | 400  |                           |     | 5         | 7.8     |

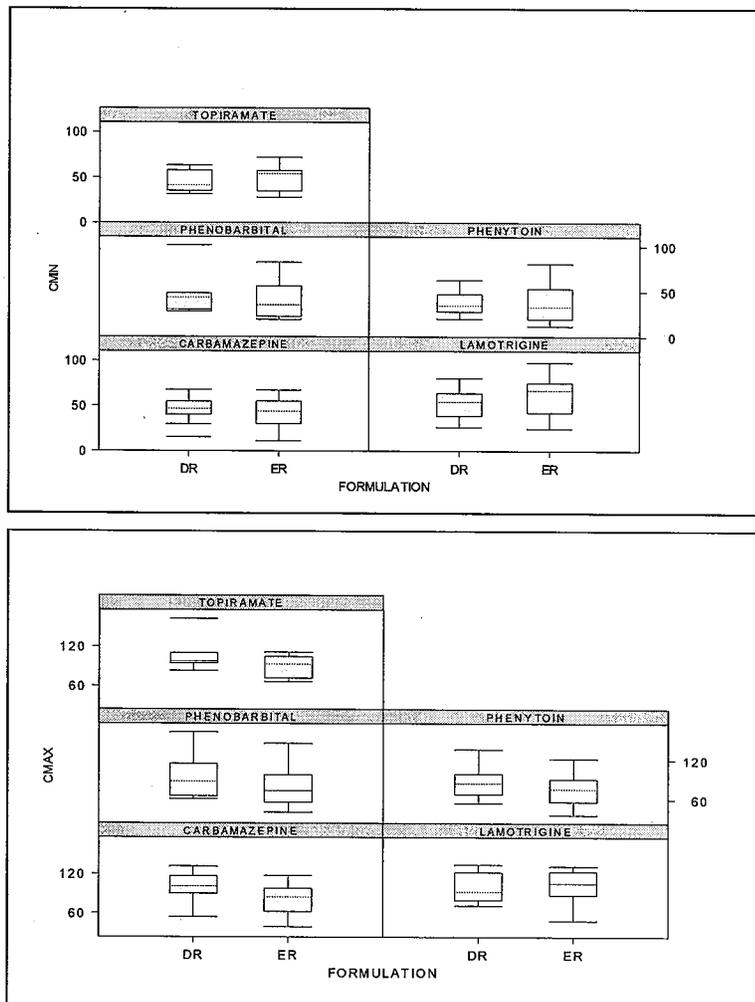
\*There was one subject of primidone, the subject was classified as a phenobarbital-user since primidone is metabolized to phenobarbitone after absorption.

An ANOVA test was conducted on the logarithm of dose normalized AUC to test the interaction between enzyme-inducing AED and the study drug regimen (ER QD or DR Q8H). The test statistic was not significant ( $p=0.2640$ )

The point estimate of ER/DR relative bioavailability for the different enzyme inducing AEDs were all acceptable (see Table above):

The following figures show the AUC, Cmax and Cmin for the ER and DR regimen, based on the coadministered enzyme inducing AED.





No specific trends could be determined in the PK parameters based on coadministered enzyme inducing AEDs. Looking at the individual C<sub>min</sub> it was found that out of the 20 subjects that had lower C<sub>min</sub> values, 10 were on phenytoin, 5 on carbamazepine, 2 on lamotrigine, 2 on phenobarbital, and 1 on topiramate. Any particular trend is not likely to be observed, as the same enzyme inducing effect of the AED would be anticipated in both ER and DR regimen.

Overall Conclusions:

- DR doses of 875-4250 mg have been compared in patients with corresponding 8-20% higher ER doses, however only 4 patients were enrolled at DR doses greater than 3000 mg.
- ER doses 8-20% higher than the DR dose were equivalent in terms of AUC, C<sub>max</sub> and C<sub>min</sub> in the dose range studied according to the statistical criteria, with the

limitation of only 4 subjects being enrolled at DR doses greater than 3000 mg. Hence, the adequacy of the data at higher doses cannot be determined.

- Looking at individual data, it was observed that six subjects had more than 2-fold lower C<sub>min</sub> for the ER regimen as compared to the DR regimen and 14 subjects (excluding the 6) had > 20% lower C<sub>min</sub> in the ER regimen as compared to the corresponding DR regimen. The low C<sub>min</sub> subjects did not belong to any particular dose group or to any particular group of patients taking the same concomitant AEDs. Although, some subjects have lower C<sub>min</sub> values for the ER formulation, they were within the population distribution of the C<sub>min</sub> values for Reference or Test. Hence, if adequate clinical response is not obtained, it would be desirable to monitor plasma valproate levels.
- The Depakote DR dose did not have an effect on the ER/DR relative bioavailability in the dose range studied.
- Concomitant enzyme inducing AEDs did not affect the ER/DR relative bioavailability in the dose range studied.

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