

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-168/S-004

MEDICAL REVIEW

Review and Evaluation of Proposed Labeling Supplement

NDA (Serial Number)	20-782 N (AZ)
	21-168 SLR-004 Labeling Supplement
Sponsor:	Abbott Laboratories
Drug:	Divalproex Sodium Extended-Release (Depakote ER)

Proposed Indication: **Epilepsy and/or conversion from *Depakote DR***

Material Submitted:

Draft Labeling for Depakote ER

Overview and Summary of the Bioavailability of Depakote ER (Report No. R&D/02/323)

Final Report M00-232: Comparison of Bioavailability of Depakote ER (1000 mg and 1500 mg total daily dose) Relative to Depakote DR (875 and 1250 mg total daily dose) in Healthy Volunteers

Final Report M01-274: Comparison of Bioavailability of Depakote Extended-Release Formulation Relative to Depakote Delayed-Release in Adult Patients with Epilepsy on a Depakote-Release Formulation and an Enzyme-Inducing Antiepileptic Drug

Also reviewed:

Depakote ER Annual Report (NDA 21-168 Y-002; correspondence date October 16, 2002)

Correspondence Date:	June 26, 2002
Date Received Agency:	June 27, 2002
Date Review Completed	November 29, 2002
Reviewer:	Philip H. Sheridan, M.D.

1. Summary

This submission proposes new labeling for Depakote ER supported by the final reports of two bioavailability studies (M00-232 and M01-274) comparing Depakote ER to Depakote DR (aka Depakote).

Currently the labeling indication for Depakote ER is restricted to adult migraine prophylaxis (for patients greater than 16 years of age). The Sponsor would like to **add to Depakote ER labeling both guidelines for conversion from Depakote DR to Depakote ER and an indication for epilepsy.** The Sponsor hopes to avoid having to conduct full-scale efficacy studies for Depakote ER in epilepsy by reference to the Depakote DR efficacy studies in epileptic patients.

After reviewing this submission and the Biopharmacology review of the submission by Dr. Veneeta Tandon, I conclude that the proposed conversion scheme is valid for adults on Depakote DR in the range of 500 mg daily to 3125 mg daily which would include most adults on either antiepileptic monotherapy or combination therapy. Fortunately, there is no evidence that the conversion factor differs between relatively low and relatively high dose Depakote DR within the dose range used by most adult patients.

For some drugs, a demonstration of bioequivalence in adults is accepted as indicative of bioequivalence in children as well. In expectation that such a consideration would be applicable to Depakote ER, the Sponsor's proposed labeling language includes an indication for children down to age 10 years for Depakote-ER since Depakote-DR has this indication.

However, there is some uncertainty in the mind of this reviewer that the same conversion factor (derived from two adult bioavailability studies) will apply to children. For example, the pediatric gastrointestinal tract might absorb Depakote ER either more or less efficiently than the adult gastrointestinal tract. The proposed labeling in this submission (Appendix 2, page 52) notes that "In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of DEPAKOTE ER tablets in the stool." The incidence might be higher in the pediatric population.

In fact, the Sponsor has previously acknowledged the uncertainty of the conversion factor for children. On January 3, 2001 during a face-to-face meeting with the Division about the limitations of Study M00-232, the Sponsor commented that children experience so much enzyme induction that conversion guidelines may be difficult and that it may be necessary to rely on therapeutic monitoring rather than a conversion factor when changing from DR to ER in children or in adults at higher DR doses. Although the subsequent Study M01-274 addressed the situation of higher DR doses in adults (up to 3,125 mg daily), it did not include any pediatric patients; the need for future pediatric studies was again stated by the Division in discussing Study M01-274 with the Sponsor on May 3, 2001.

Moreover, there will presumably be more pediatric pharmacokinetic data concerning Depakote ER available in the near future. At present, Study M01-313 (Evaluation of pharmacokinetic profile and safety of Depakote extended release tablets in pediatric patients) is studying 12 children age 8-11 years and 12 adolescents age 12-17 years. Although the Depakote ER pediatric patients will not be epileptic patients, the results of the study are expected to be applicable to epileptic patients in this age range.

The anticipated results of this study (M01-313) were specifically taken into account when the Division formulated the Pediatric Written Request letter (August 9, 2002). This Written Request includes the Pharmacokinetic Study in Pediatric Patients (3-17 years of age). The stated objective for this requested study (or studies) is "to characterize the pharmacokinetics of valproate in the pediatric patient population to determine age-appropriate dosing regimens in the pediatric efficacy and safety studies for the different indications described in this Written Request." In consideration of the anticipated results of M01-313, the Written Request further states "The pharmacokinetics of valproate must be evaluated after Depakote ER administration in patients aged 8 - 17 years or lower, if the lower age limit specified in the inclusion criteria of the efficacy/safety study is <8 years." This statement acknowledges that M01-313 data (including children down to age 8) will potentially satisfy some of the pharmacokinetic study requirements of the Written Request (although the pediatric partial seizures efficacy and safety study proposed later in the text of the Written Request involves patients aged 3 years to 10 years and thus will require that the Sponsor first obtain further pharmacokinetic data down to age 3 years before choosing a dose regimen for the study).

It is true that the Pediatric Written Request Pharmacokinetics section also contains the statement that "If different formulations will be used in the clinical trials, the relative bioavailability between the formulations must be established or known (*the use of bioavailability data generated in adults is acceptable*)" [italics added by this reviewer]. However, to this reviewer, the total context for the Written Request including the statements quoted in the previous paragraph make this "*use of bioavailability . . . acceptable*" clause applicable to the equivalence among Depakote DR, Depakote Sprinkle capsules, and Depakene rather than to the inter-conversion between Depakote DR and Depakote ER. The conversion factor in children under age 17 years down to age 10 years (or 3 years) may not be the same as it is in adults

Therefore, it seems prudent to this reviewer to confine the Depakote ER labeling to the adult population above age 18. This would be consistent with the *Warnings – Hepatotoxicity* section where the proposed labeling (Appendix 2, Page 34) does not change the current Depakote ER labeling which states "The use of DEPAKOTE ER in children is not recommended". This would also be consistent with the *Pediatric Use* section where the proposed labeling (Appendix 2, page 43) does not change the current Depakote ER labeling which states "Safety and effectiveness of

DEPAKOTE ER in the prophylaxis of migraine in pediatric patients have not been established. Because of the known risks of valproate therapy in pediatric patients when used for other conditions, the use of DEPAKOTE ER in this population is not recommended." [It should be noted that the Sponsor presumably wrote the sentence about migraine just quoted because neither Depakote DR not Depakote ER have been tested for efficacy in migraine prophylaxis in patients less than 16 years of age; the Sponsor was presumably not commenting on the conversion of Depakote DR to Depakote ER in children.] This would also be consistent with the *Drug Interactions* section where the proposed labeling (Appendix 2, page 39) does not change the current Depakote ER labeling which, in the context of interaction with aspirin, states "Depakote ER is not indicated for use in children".

If the new DEPAKOTE ER labeling does restrict the epilepsy indication to adults, pediatric data under the Pediatric Rule or its operative equivalent (deferred for the two bioavailability studies M00-232 and M01-274) will need to be obtained from future studies (specifically, the ongoing M01-313 and the future pharmacokinetic studies presumably to be done in response to the August 9, 2002 Pediatric Written Request that calls for efficacy/safety studies for partial seizures, migraine, and mania).

Overall Conclusions

The conversion factor, originally derived from seven bioavailability studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) comparing equal doses of Depakote ER and Depakote DR, has been confirmed in study M00-232 in adult volunteers and in M01-274 in adult epileptic patients.

Study M00-232 in adult volunteers indicates the conversion scheme is appropriate for Depakote monotherapy up to 1250 mg/day.

Study M01-274 in adult epileptic patients on a variety of concomitant antiepileptic drugs over a Depakote DR range up to 3,125 mg/day indicates that the conversion scheme is appropriate for most adults on either antiepileptic monotherapy or combination therapy.

Therefore, Depakote ER can be given the same epilepsy indication as Depakote DR in adults.

The Sponsor proposes that Depakote ER have the same epilepsy indication as Depakote DR in children as well. However, since it is not known if the adult conversion factor would be the same for children, further studies are needed.

Given that only sparse data is available for doses of Depakote above 3,125 mg daily, the proposed labeling for dose conversion should be reworded to indicate that

at higher Depakote-DR dosages there is insufficient data to allow conversion dose recommendations.

The Sponsor should determine if redesigning the Depakote-ER bottle and blister label (making "ER" and "Extended Release" bright red) has effectively prevented prescribing and dispensing errors since such errors might otherwise increase if Depakote ER is given the epilepsy indication.

2. Introduction

Currently the labeling indication for Depakote ER is restricted to migraine prophylaxis for adults. The Sponsor would like to add to Depakote ER labeling both **guidelines for conversion from Depakote DR to Depakote ER** and an **indication for epilepsy**. The Sponsor hopes to avoid having to conduct full-scale efficacy studies for Depakote ER in epilepsy by reference to the Depakote DR efficacy studies in epileptic patients.

Seven previous bioavailability studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) comparing equal doses of Depakote ER and Depakote DR have indicated that equivalent doses of Depakote ER resulted in 15-20% less AUC compared to Depakote DR.

Because of the lack of simple bioequivalence between equal doses of Depakote ER and Depakote DR, the Division issued a not-approvable letter on June 17, 1998 for NDA 20-782 (Depakote ER Tablets 500 mg). This NDA had sought approval for Depakote ER for the treatment of epilepsy. The Division was specifically concerned that, if epileptic patients used Depakote ER, the Cmin of Depakote ER might drop below the Cmin of the equivalent dose of Depakote DR and thus allow breakthrough of seizures after conversion from DR to ER.

Subsequently, on August 4, 2000, the Division approved NDA 21-168 that provided a clinical efficacy study that demonstrated the safety and effectiveness of Depakote ER for prophylaxis of migraine headaches in adults.

Returning to the epilepsy indication for Depakote ER, the Sponsor designed a comparison of bioavailability protocol (**M00 232 in normal volunteers**) [**submitted as IND 47,714 Serial No. 023 by the Sponsor on October 12, 2000**] to justify labeling for Depakote ER (under NDA 21-168) addressing conversion from Depakote DR to Depakote ER.

MOO-232 was a Phase I multiple-dose, titration, fasting, randomized, open-label, single-center, crossover, five-period study. For one comparison, the ratio of the daily doses was 8:7 (1000 mg ER versus 875 mg DR) and for the other comparison, the ratio was 6:5 (1500 mg ER versus 1250 mg DR). Each patient

made sequential crossovers into each of these dose periods by moving through five sequential periods.

On December 7, 2000, the Division had an internal meeting about "proposed" protocol M00-232 raising the following concerns:

- a) The high dose arm [comparing Depakote DR 1250 (given as 625 mg po **BID**) to Depakote 1500mg (given QD)] could lead to unsafe high plasma concentrations
- b) The low dose arm [comparing Depakote DR 875 mg (given as 500 mg po qAM and 375 mg po qPM) to Depakote ER 1000 mg (given as a single QD dose)] may not be a valid comparison since the DR scheme of administration might lower the Cmin to which Depakote ER is compared. A better comparison would come from switching Depakote DR to 375-mg qAM and 500 mg qPM.
- c) Even assuming that M00232 succeeded
 - The nonlinearity of Depakote pharmacokinetics would only justify labeling addressing dosing as high as the equivalent of Depakote DR 1250 mg given at BID intervals (not TID or QID).
 - Depakote DR TID or QID intervals would lead to higher Cmin and lower Cmax than BID and would be a harder target for the ER formulation to approximate.
 - The labeling would not apply to patients who are on other drugs (e.g. EIAED's) that affect the pharmacokinetics of divalproex sodium.
 - If the conversion factor is different for low vs. high dose Depakote DR, what could be said about intermediate doses?

After the meeting, the Sponsor informed the Division that study M00-232 had in fact already been completed. This Study is discussed in detail below in Section 3.

A face-to face meeting was held with the Sponsor January 3, 2001.

In response to the Division concerns, the Sponsor made the following points.

- ◆ It is difficult to do Depakote DR studies with q6h or TID dosing because staggering the meals and doses becomes too complicated.
- ◆ Also, if the labeling gave a conversion from q6h DR to ER, there may be an overshoot because many of the q6h DR patients are frequently missing doses.
- ◆ According to a recent survey of usage, 40% of patients on Depakote for epilepsy use TID dosing, 28.6% use BID dosing, 9.1% use QID dosing, and 21.4% are not known. A q6h study was included in the 1996 IND submission (22 subjects showing an ER/DR ratio for AUC of .94).

- ◆ The Sponsor believes on the basis of preclinical epilepsy models that that total daily systemic exposure (AUC) is more important than Cmin for antiepileptic efficacy.
- ◆ In any event, as long as Cmin with ER (whenever it comes) is higher than Cmin with DR (whenever it comes), antiepileptic efficacy should be maintained. (The Division replied that Cmin would be defined as the lowest level at any time during the day; with this operational definition, not being able to equally divide a TID daily dose of Depakote would not be a problem.)
- ◆ Pharmacokinetic studies require a large quantity of blood especially if unbound levels are included. A simulation of free levels could be used.
- ◆ Most adults take DR doses in the 500-1500 mg/day range rather than higher daily doses. Therefore it would be hard to recruit patients in the higher dose ranges. [The Division pointed out that this would limit the conversion to ER labeling to a subset of approved DR doses since adults as well as children may require as much as 60 mg/kg/day.]
- ◆ Children experience so much enzyme induction that conversion guidelines would be difficult. It may be necessary to rely on therapeutic monitoring rather than a conversion factor when changing from DR to ER in children or adults at higher doses.

Preliminary results from M00-232 were also presented at the January 3, 2001 meeting. The pharmacokinetic comparisons of daily doses were done with ratios of 8:7 (1000 mg Depakote ER versus 875 mg Depakote DR) and 6:5 (1500 mg Depakote ER versus 1250 mg Depakote DR). The DR was given in BID dosage and the ER in QD dosage. Similar AUC's were obtained from the Depakote ER regimens compared to the Depakote DR regimens. For both dose ranges, the Cmax of the Depakote ER regimen was less and the Cmin of the Depakote ER regimen was more than was achieved by the corresponding Depakote DR regimen. [The final report of M00-232 is discussed below in section 3].

In light of the discussion with the Division, the Sponsor planned to design a protocol studying adult epilepsy patients at a wide range of Depakote q8h doses and on concomitant EIAED's. This study was ultimately done as Study M01-274 (discussed below in Section 4).

Another meeting with the Sponsor on May 3, 2001 to review the draft protocol for M01-274 is discussed below at the beginning of Section 4.

In general, the Division has not allowed efficacy labeling of a new formulation unless either (1) true bioequivalence to a marketed drug of proven efficacy is established or (2) efficacy is established independently for the new formulation.

However, the Division addressed the issue with regard to Depakote ER during the January 3, 2001 meeting with the Sponsor in light of the preliminary M00-232 report

presented at that time. The Division indicated that it was theoretically possible to obtain an epilepsy indication based on pharmacokinetic studies if these studies showed a predictably comparable performance of daily Depakote ER (as compared to Depakote DR) across the extremes of dose range and dose frequency in the current Depakote DR labeling. The daily Depakote ER dosage should show decreased fluctuation and equivalent AUC compared to the reference Depakote DR.

In this current submission, the Sponsor states that the combined results of **M00-232** and **M01-274** satisfy this requirement.

Financial Disclosure Statements for Studies M00-232 and M01-274:

Study M00-232 was a single center study conducted by Laura A. Williams, MD, MPH, Director, Abbott Clinical Pharmacology Research Unit.

_____, a sub-investigator for M00-232, disclosed an equity interest in Abbott in excess of _____, but his involvement was limited to routine physical examinations of subjects.

Study M01-274 had five study sites (four of which enrolled patients) under the overall direction of _____ Coordinating Investigator.

Dr. James C. Cloyd, a principal investigator for M01-274 received a significant payment from Abbott in excess of _____ after February 2, 1999, but his Center did not enroll any patients

I have reviewed the *Disclosure Statements for Financial Interests and Arrangements of Clinical Investigators* for Studies M00-232 and M01-274. I conclude that there is no apparent potential influence on the studies' conduct and results from these financial interests and arrangements.

3. Study M00-232 Comparison of Bioavailability of Depakote ER (1000 mg and 1500 mg total daily dose) Relative to Depakote DR (875 and 1250 mg total daily dose) in Healthy Volunteers

3.1 Objective

Primary: Pharmacokinetic comparison of Depakote ER formulation QD regimens to regular Depakote DR formulation BID regimens, with larger total daily doses for the ER formulation regimens. For one comparison, the ratio of the daily doses will be

8:7 (1000 mg ER versus 875 mg DR) and for the other comparison, the ratio will be 6:5 (1500 mg ER versus 1250 mg DR).

Secondary: Comparison of the ER and DR regimens with respect to safety and tolerability.

3.2 Design

Phase I, multiple-dose, titration, fasting, randomized, open-label, single-center, cross-over, five-period study. The five sequential periods were a baseline of either 500 mg DR or 500 mg ER followed either by one period each of 1000 mg ER, 875 mg DR, 1250 mg DR, and 1500mg ER or by one period each of 875 mg DR, 1000 mg ER, 1500 mg ER, and 1250 mg DR. The five periods were not separated by a washout period and consisted of both confinement and non-confinement segments. Following the five dosing periods, the dose was tapered for 5 days.

3.3 Sample Size

35 healthy volunteers

Sequence 1 had 15 men and 3 women; Sequence 2 had 8 men and 9 women.

3.4 Key Inclusion Criteria

Age 18 to 55 years

Good health (screening procedures performed within 28 days of study initiation include medical history, physical exam, vital signs, laboratory profile, and EKG.)

3.5 Key Exclusion Criteria

Female patients of childbearing potential unless total abstinence or reliable birth control method

Female patients who were breastfeeding

Positive pregnancy test at screening or on day prior to drug administration

Use of nicotine products in 6 months prior to study

3.6 Concomitant Medications

None.

3.7 Dosage

For one comparison, the ratio of the daily doses was 8:7 (1000 mg ER versus 875 mg DR) and for the other comparison, the ratio was 6:5 (1500 mg ER versus 1250 mg DR). Each patient crossed-over sequentially into each of these dose periods.

3.8 Outcome Measure

For each comparison of an ER QD regimen to a regular DR BID regimen, an analysis of variance for a crossover design was performed for the logarithm of AUC 0-24, the logarithm of C_{max}, C_{min}, and DFL. A two one-sided tests procedure was performed for AUC 0-24 via a 90% confidence for the ratio of central values with 0.80 to 1.25 as the range of equivalence. One-sided tests were performed for C_{max} and C_{min}.

3.9 Analysis

Pharmacokinetic: C_{max}, AUC 0-24, C_{min} and degree of fluctuation (DFL).

3.10 Safety Monitoring

Vital signs, laboratory testing, physical examinations, ECG, and adverse event monitoring.

The pharmacokinetic comparisons of daily doses were done with ratios of 8:7 (1000 mg Depakote ER versus 875 mg Depakote DR) and 6:5 (1500 mg Depakote ER versus 1250 mg Depakote DR). The DR was given in BID dosage and the ER in QD dosage. Similar AUC's were obtained from the Depakote ER regimens compared to the Depakote DR regimens. For both dose ranges, the C_{max} of the Depakote ER regimen was less and the C_{min} of the Depakote ER regimen was more than was achieved by the corresponding Depakote DR regimen.

The mean pharmacokinetic profiles for the 100 mg ER/875 mg DR regimen and the 1500 mg ER/1250 mg DR regimen are shown below in Figure 1.

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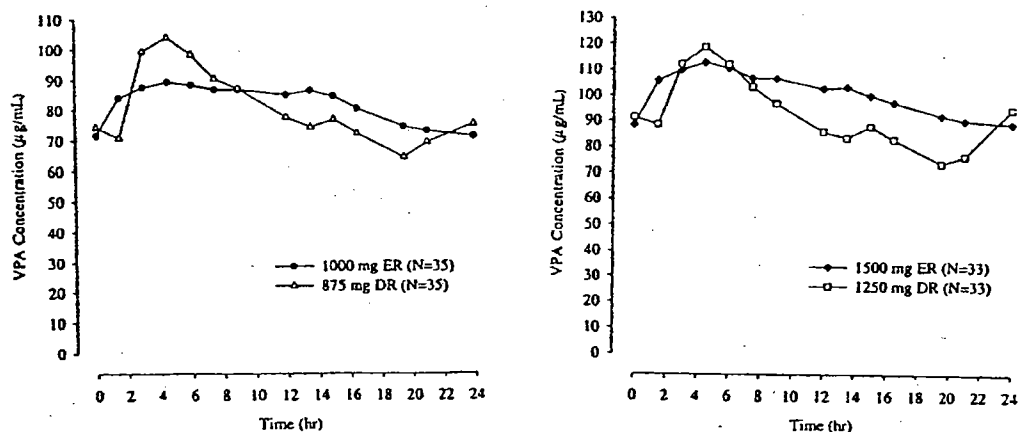


Figure 1: Mean Plasma Concentration-Time Profiles for Depakote ER vs. Depakote DR from Protocol M00-232 in normal volunteers.

The overall conclusion from the Division's Biopharmacology Reviewer was "In healthy volunteers for 875 mg DR/ 1000 mg ER and 1250 mg DR/1500 mg ER comparisons, equivalence was established between for AUC, C_{max}, and C_{min}. Depakote ER DFL [degree of fluctuation] was lower than Depakote DR DFL."

There were no unexpected or serious adverse events attributable to the Depakote DR or Depakote ER. There were no deaths during the study.

Reviewer's Comments:

M00-232 alone did not justify labeling for conversion of DR to ER or labeling for ER use in epilepsy. The use of BID Depakote DR regimens in this study (rather than QID dosage) made it easier for ER to have comparable AUC, C_{max}, and C_{min}. Also, the study really only addressed conversion from Depakote DR **monotherapy** since the subjects were not on concomitant antiepileptic drugs.

Furthermore, the highest Depakote DR dose was 1250 mg in M00-232, and epileptic patients on combination therapy routinely take doses twice this magnitude. The nonlinear protein binding of valproate may or may not change the conversion factor at the higher end of the dosing spectrum. Therefore, the Division recommended using unbound and bound valproate levels in a second study (M00-274 below).

Concern also remained about the generalizability of results to epileptic patients on EIAED's. One clinical concern was that the C-min might drop after conversion from DR to ER in a patient on a concomitant EIAED and result in breakthrough seizures if the epilepsy indication were added to Depakote ER labeling.

In a face-to-face meeting with the Sponsor on January 3, 2001, the Division suggested that, if the Sponsor were successful in demonstrating that the conversion from Depakote DR to Depakote ER could be made in patients with maintenance of comparable Cmin, Cmax, and AUC (using unbound and bound valproate levels) by the use of a reliable conversion factor over the full clinically-used range of DR dosing, then adding epilepsy to the labeled indications for Depakote ER might not require an efficacy trial.

The Sponsor responded by proposing **Study M01-274** of epileptic patients on Depakote DR who would convert to Depakote ER (while remaining on concomitant EIAED therapy).

4. Protocol M01-274 Comparison of Bioavailability of Depakote Extended-Release Formulation Relative to Depakote Delayed-Release in Adult Patients with Epilepsy on a Depakote-Release Formulation and an Enzyme-Inducing Antiepileptic Drug

On May 3, 2001, a face-to face meeting was held between the Sponsor and the Division. The Division found the draft protocol for M01-274 was acceptable. The Division noted that the study could be done with the 500-mg tablet of Depakote-ER (using the dose conversion chart proposed (Appendix 1) but that a 250 mg preparation should be developed before a such a dose conversion would be proposed for labeling. The Division also stated that:

- If only sparse data was available for conversion from higher doses, the labeling might be restricted to the dose range for which there is adequate data.
- Data relevant to each specific concomitant AED should be provided.
- Recommendations for converting Depakote DR monotherapy to Depakote ER monotherapy could be based on Study M00-232.
- The Sponsor should address the several reports of dispensing and/or prescribing errors associated with Depakote DR and ER.

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[The Sponsor has since redesigned the Depakote ER 500 bottle and blister labels to increase the prominence of "ER" and "Extended Release" and to make them appear different from the current Depakote –DR labels. "ER" and "Extended Release" on the Depakote-ER labels are now in bright red. Examples are included in the Annual Report for Depakote-ER submitted October 16, 2002. The Sponsor still needs to determine whether this will be effective in preventing errors.]

- Pediatric data under the Pediatric Rule would be deferred for Study M00-274 but would need to be addressed in the future.

4.1 Objective

Primary: Pharmacokinetic comparison of Depakote ER formulation QD regimens to regular Depakote DR formulation Q8H regimens (using Depakote ER doses that were 8-20% greater than the corresponding Depakote total daily DR doses) in patients with epilepsy currently receiving Depakote-DR and one EIAED (CBX, LTG, OXYCARB, PB, PHT, PRIM, or TPM).

Secondary: Comparison of the ER and DR regimens with respect to safety and tolerability.

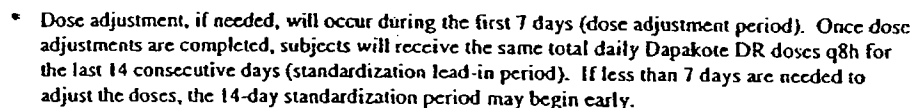
4.2 Design

This Phase I, multiple-dose, modified fasting, randomized, open-label, multi-center study was conducted according to a two-period, crossover design. The subjects had their Depakote DR converted to a standardized q8h regimen (Appendix I) upon entry into the lead in period beginning Study Day-21 and including a 7 day "dose adjustment period") and were maintained on a standardized daily dose of Depakote DR q8h for 14 consecutive days (a 14 day standardization period from Study Day-14 through Study Day-1).

Subjects were then randomized to the two regimen sequences and received their standardized Depakote DR q8h regimen during one study period and their corresponding Depakote ER QD regimen in the morning during the other study period. The daily mg-dose of Depakote ER was 8-20% greater than the Depakote DR total daily dose.

Subjects were confined from Study Day 5 through the 24-hour blood collection on Study Day 8 and from Study Day 12 through the 24-hour blood collection on Study Day 15. No grapefruit products or caffeine were allowed during the confinement periods. There was no washout interval between the two study periods.

Screening	Lead-In Period*		Randomized Regimen Sequences	
	Dose Adjustment Period	Standardization Period		
			Period 1	Period 2
		Depakote DR Q8H	Sequence 1: Depakote DR Q8H	Depakote ER QD
			Sequence 2: Depakote ER QD	Depakote DR Q8H



Female patients who were breastfeeding

Positive pregnancy test at screening or on day prior to drug administration

Use of nicotine products in 6 months prior to study

4.6 Concomitant Medications

No OTC or prescription medications that could confound the interpretation of study results were allowed from 2 weeks prior to the standardization lead in period until after study completion.

4.7 Dosage

Oral Depakote DR tablets (125 mg, 250mg, 500 mg) and oral Depakote-ER tablets (500 mg) were used. During the "Dose Adjustment Period", each individual patient's entry Depakote DR dosage were adjusted to conform to one of the Depakote DR TID regimens shown in Appendix I of the protocol (appended to end of this review). During the "Randomized Regimen Sequences", there was a crossover between the corresponding Depakote-DR and Depakote -ER doses as indicated in Appendix I. On a mg basis, each Depakote ER dose exceeded the corresponding Depakote DR dose by 8 – 20%.

4.8 Outcome Measure

Efficacy: No data collected

Pharmacokinetic: C-max, T-max, C-min, AUC 0-24h, C-min and degree of fluctuation (DFL) from Study Days 7 and 14 data.

Safety: Adverse events, vital signs, physical examination, and laboratory test assessments. Although the proposed study does not determine efficacy, a seizure count was maintained in the event that an exacerbation of seizure frequency occurred as an adverse event.

4.9 Analysis

In the primary analysis, Depakote ER and Depakote DR were compared in a conventional analysis of variance for a crossover design. In this analysis, the study subjects were viewed as a single sample and were not classified by Depakote dose level. Within the framework of this primary analysis, the two one-sided tests procedure was performed for AUC, and a one-sided test was performed for C-min

with the aim of showing non-inferiority of the ER formulation. Another analysis was performed to explore whether the availability of the ER formulation relative to that of Depakote DR q8h depends upon the Depakote dose.

4.10 Safety Monitoring

Vital signs, laboratory testing, physical examinations, ECG, and adverse event monitoring.

4.11 Results

Because of concern that nonlinear protein binding of valproate might change the conversion factor at the higher end of the dosing spectrum, the Division had originally recommended that both unbound and bound valproate levels be done during this study. However, in this submission, the Sponsor argues that unbound levels were not necessary because the Sponsor presents an equation describing the relationship between total and free concentrations of valproic acid. The equation was based on Study M98-938 in NDA 20-593, S006 and included an upper range of total level 150 mcg/ml. The Biopharmacology reviewer, Dr. Veneeta Tandon, deemed this equation acceptable in her Biopharmacology review.

After several discussions with Dr. Vaneeta Tandon, I concur with her conclusions as follows:

- "Depakote DR doses of 875-4250 mg have been compared in patients with corresponding 8-20% higher Depakote ER doses; however only 4 patients were enrolled at Depakote DR doses greater than 3000 mg.
- ER doses 8-20% higher than the DR dose were equivalent in terms of AUC, C_{max}, and C_{min} 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 a 2-fold lower C_{min} for the ER regimen as compared to the corresponding DR regimen and 14 subjects (excluding the 6) had > 20% lower C_{min} in the ER regimen as compared to the corresponding DR regimen. The low C_{min} 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_{min} values for the ER formulation, they were within the population distribution of the C_{min} values for Reference or Test. Hence, if an adequate clinical response is not obtained, it would be desirable to monitor plasma valproate levels.

- The Depakote DR dose does 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."

With regard to safety and tolerability, there were no seizure exacerbations, no unexpected or serious adverse events attributable to the antiepileptic medications, and no deaths. Specifically, the patients who had lower Cmin values on Depakote ER did not have break-through seizures.

4.12 Reviewer's Comments on M01-274:

Fortunately, it appears that the conversion factor from earlier studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) that was confirmed in study M00-232 in volunteers (appropriate for Depakote monotherapy up to 1250 mg/day) is also confirmed in M01-274 in epileptic patients on a variety of concomitant antiepileptic drugs over a Depakote DR range up to 3125 mg/day.

Although some patients were noted to have lower Cmin values after conversion to Depakote-ER, they did not have breakthrough seizures. This is consistent with the Sponsor's statement at the January 3, 2001 meeting with the Division that preclinical epilepsy models suggest that total daily systemic exposure to valproate (the AUC) is more important than Cmin for antiepileptic efficacy. Of course, clinicians will probably continue to use "trough levels" when wishing to verify an adequate valproate level in a patient since "trough levels" are more reproducible than random or near-peak levels. For most patients this would not be expected to be a problem.

A larger question for the Division to consider in the future is whether bioequivalence studies of antiepileptic drugs in general should usually require equivalent Cmin's. Bioequivalent studies are often single dose studies that thus don't have Cmin's (which requires a multiple dose paradigm).

The dose conversion table (Appendix I) used in M01-274 requires at some doses that patients either raise or lower their dose of Depakote DR in order to convert to

ER. This was acceptable during the study but would not be appropriate in labeling for clinical practice. Therefore, the Sponsor has developed 250-mg tablets of Depakote ER that has been approved for marketing.

5. Reviewer's Comments on Proposed Labeling

Currently the labeling indication for Depakote ER is restricted to adult migraine prophylaxis (for patients greater than 16 years of age). The Sponsor would like to **add to Depakote ER labeling both guidelines for conversion from Depakote DR to Depakote ER and an indication for epilepsy.** The Sponsor hopes to avoid having to conduct full-scale efficacy studies for Depakote ER in epilepsy by reference to the Depakote DR efficacy studies in epileptic patients.

After reviewing this submission and the Biopharmacology review of the submission by Dr. Veneeta Tandon, I conclude that the proposed conversion scheme is valid for adults on Depakote DR in the range of 500 mg daily to 3,125 mg daily which would include most adults on either antiepileptic monotherapy or combination therapy. Fortunately, there is no evidence that the conversion factor differs between relatively low and relatively high dose Depakote DR within the dose range used by most adult patients.

For some drugs, a demonstration of bioequivalence in adults is accepted as indicative of bioequivalence in children as well. In expectation that such a consideration would be applicable to Depakote ER, the Sponsor's proposed labeling language includes an indication for children down to age 10 years for Depakote-ER since Depakote-DR has this indication.

However, there is some uncertainty in the mind of this reviewer that the same conversion factor (derived from two adult bioavailability studies) will apply to children. For example, the pediatric gastrointestinal tract might absorb Depakote ER either more or less efficiently than the adult gastrointestinal tract. The proposed labeling in this submission (Appendix 2, page 52) notes that "In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of DEPAKOTE ER tablets in the stool." The incidence might be higher in the pediatric population.

In fact, the Sponsor has previously acknowledged the uncertainty of the conversion factor for children. On January 3, 2001 during a face-to-face meeting with the Division about the limitations of Study M00-232, the Sponsor commented that children experience so much enzyme induction that conversion guidelines may be difficult and that it may be necessary to rely on therapeutic monitoring rather than a conversion factor when changing from DR to ER in children or in adults at higher DR

doses. Although the subsequent Study M01-274 addressed the situation of higher DR doses in adults (up to 3,125 mg daily), it did not include any pediatric patients; the need for future pediatric studies was again stated by the Division in discussing Study M01-274 with the Sponsor on May 3, 2001.

Moreover, there will presumably be more pediatric pharmacokinetic data concerning Depakote ER available in the near future. At present, Study M01-313 (Evaluation of pharmacokinetic profile and safety of Depakote extended release tablets in pediatric patients) is studying 12 children age 8-11 years and 12 adolescents age 12-17 years. Although the Depakote ER pediatric patients will not be epileptic patients, the results of the study are expected to be applicable to epileptic patients in this age range.

The anticipated results of this study (M01-313) were specifically taken into account when the Division formulated the Pediatric Written Request letter (August 9, 2002). This Written Request includes the Pharmacokinetic Study in Pediatric Patients (3-17 years of age). The stated objective for this requested study (or studies) is "to characterize the pharmacokinetics of valproate in the pediatric patient population to determine age-appropriate dosing regimens in the pediatric efficacy and safety studies for the different indications described in this Written Request." In consideration of the anticipated results of M01-313, the Written Request further states "The pharmacokinetics of valproate must be evaluated after Depakote ER administration in patients aged 8 - 17 years or lower, if the lower age limit specified in the inclusion criteria of the efficacy/safety study is <8 years." This statement acknowledges that M01-313 data (including children down to age 8) will potentially satisfy some of the pharmacokinetic study requirements of the Written Request (although the pediatric partial seizures efficacy and safety study proposed later in the text of the Written Request involves patients aged 3 years to 10 years and thus will require that the Sponsor first obtain further pharmacokinetic data down to age 3 years before choosing a dose regimen for the study).

It is true that the Pediatric Written Request Pharmacokinetics section also contains the statement that "If different formulations will be used in the clinical trials, the relative bioavailability between the formulations must be established or known (*the use of bioavailability data generated in adults is acceptable*)" [italics added by this reviewer]. However, to this reviewer, the total context for the Written Request including the statements quoted in the previous paragraph make this "*use of bioavailability . . . acceptable*" clause applicable to the equivalence among Depakote DR, Depakote Sprinkle capsules, and Depakene rather than to the inter-conversion between Depakote DR and Depakote ER. The conversion factor in children under age 17 years down to age 10 years (or 3 years) may not be the same as it is in adults

Therefore, it seems prudent to this reviewer to confine the Depakote ER labeling to the adult population above age 18. This would be consistent with the *Warnings* –

Hepatotoxicity section where the proposed labeling (Appendix 2, page 34) does not change the current Depakote ER labeling which states "The use of DEPAKOTE ER in children is not recommended". This would also be consistent with the *Pediatric Use* section where the proposed labeling (Appendix 2, page 43) does not change the current Depakote ER labeling which states "Safety and effectiveness of DEPAKOTE ER in the prophylaxis of migraine in pediatric patients have not been established. Because of the known risks of valproate therapy in pediatric patients when used for other conditions, the use of DEPAKOTE ER in this population is not recommended." [It should be noted that the Sponsor presumably wrote the sentence about migraine just quoted because neither Depakote DR not Depakote ER have been tested for efficacy in migraine prophylaxis in patients less than 16 years of age; the Sponsor was presumably not commenting on the conversion of Depakote DR to Depakote ER in children.] This would also be consistent with the *Drug Interactions* section where the proposed labeling (Appendix 2, page 39) does not change the current Depakote ER labeling which, in the context of interaction with aspirin, states "Depakote ER is not indicated for use in children".

If the new DEPAKOTE ER labeling does restrict the epilepsy indication to adults, pediatric data under the Pediatric Rule or its operative equivalent (deferred for the two bioavailability studies M00-232 and M01-274) will need to be obtained from future studies (specifically, the ongoing M01-313 and the future pharmacokinetic studies presumably to be done in response to the August 9, 2002 Pediatric Written Request that calls for efficacy/safety studies for partial seizures, migraine, and mania).

Appendix 2 is the current Depakote ER labeling marked up by the Sponsor to show the Sponsor's proposed changes. I have indicated where the Sponsor's proposed changes should be modified as discussed in this section 5 of this review.

6. Conclusions

The conversion factor, originally derived from seven bioavailability studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) comparing equal doses of Depakote ER and Depakote DR, has been confirmed in study M00-232 in adult volunteers and in M01-274 in adult epileptic patients.

Study M00-232 in adult volunteers indicates the conversion scheme is appropriate for Depakote monotherapy up to 1250 mg/day.

Study M01-274 in adult epileptic patients on a variety of concomitant antiepileptic drugs over a Depakote DR range up to 3,125 mg/day indicates that the conversion scheme is appropriate for most adults on either antiepileptic monotherapy or combination therapy.

Therefore, Depakote ER can be given the same epilepsy indication as Depakote DR in adults.

The Sponsor proposes that Depakote ER have the same epilepsy indication as Depakote DR in children as well. However, since it is not known if the adult conversion factor would be the same for children, further studies are needed.

The dose conversion table (Appendix I) used in M01-274 requires at some doses that patients either raise or lower their dose of Depakote DR in order to convert to ER. This was acceptable during the study but would not be appropriate in labeling for clinical practice. Therefore, the Sponsor has developed 250-mg tablets of Depakote ER that will be marketed in the near future.

Given that only sparse data is available for doses of Depakote above 3,125 mg daily, the proposed labeling for dose conversion should be reworded to indicate that at higher Depakote-DR dosages there is insufficient data to allow conversion dose recommendations.

The Sponsor should determine if redesigning the Depakote-ER bottle and blister label (making "ER" and "Extended Release" bright red) has effectively prevented prescribing and dispensing errors since such errors might otherwise increase if Depakote ER is given the epilepsy indication.

Philip Sheridan, M. D.
Medical Reviewer

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ON ORIGINAL**

Appendix I

Total Daily Depakote DR and Corresponding Depakote ER Doses

Depakote DR Regimen				Depakote ER Regimen	
Total Daily DR Dose	Morning	Mid-Day	Evening	Daily ER Dose	% Increase
750	Titrate total daily DR doses down 125 mg during the lead-in period			1000	14.3
875	250	250	375		
1000	Titrate total daily DR doses down 125 mg or up 250 mg during the dose adjustment period				
1125	Titrate total daily DR doses up 125 mg during the lead-in period				
1250	375	375	500	1500	20.0
1375	375	500	500	1500	9.1
1500	Titrate total daily DR doses down 125 mg or up 250 mg during the dose adjustment period				
1625	Titrate total daily DR doses up 125 mg during the lead-in period				
1750	500	625	625	2000	14.3
1875	Titrate total daily DR doses down 125 mg or up 250 mg during the dose adjustment period				
2000	Titrate total daily DR doses up 125 mg during the lead-in period				
2125	625	750	750	2500	17.6
2250	750	750	750	2500	11.1
2375	Titrate total daily DR doses down 125 mg or up 125 mg during the dose adjustment period				
2500	750	875	875	3000	20.0
2625	875	875	875	3000	14.3
2750	875	875	1000	3000	9.1
2875	Titrate total daily DR doses down 125 mg or up 125 mg during the dose adjustment period				
3000	1000	1000	1000	3500	16.7
3125	1000	1000	1125	3500	12.0
3250	Titrate total daily DR doses down 125 mg or up 125 mg during the dose adjustment period				
3375	1125	1125	1125	4000	18.5
3500	1125	1125	1250	4000	14.3
3625	1125	1250	1250	4000	10.3
3750	1250	1250	1250	4500	20.0
3875	1250	1250	1375	4500	16.1
4000	1250	1375	1375	4500	12.5
4125	1375	1375	1375	4500	9.1
4250	1375	1375	1500	5000	17.6
4375	1375	1500	1500	5000	14.3
4500	1500	1500	1500	5000	11.1
4625	1500	1500	1625	5500	18.9
4750	1500	1625	1625	5500	15.8
4875	1625	1625	1625	5500	12.8
5000	1625	1625	1750	5500	10.0
5125	1625	1750	1750	6000	17.1
5250	1750	1750	1750	6000	14.3
5375	1750	1750	1875	6000	11.6
5500	1750	1875	1875	6000	9.1
5625	1875	1875	1875	6500	15.6
5750	1875	1875	2000	6500	13.0
5875	1875	2000	2000	6500	10.6
6000	2000	2000	2000	6500	8.3

APPEARS THIS WAY
ON ORIGINAL

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

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/s/

Philip Sheridan
12/18/02 03:47:04 PM
MEDICAL OFFICER

John Feeney
12/19/02 12:24:00 PM
MEDICAL OFFICER
concur; see my review

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: December 11, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-782

SUBJECT: Action Memo for NDA 20-782, for the use of Depakote ER in patients with epilepsy

NDA 20-782, for the use of Depakote ER in patients with epilepsy, was submitted to the Agency on 6/16/97 (Depakote ER is approved for use in migraine; that approval was based on controlled trials in that indication). The sponsor proposed to gain approval on the basis of a demonstration that Depakote ER, given once a day, was bioequivalent (equivalent AUC, C_{max}, and C_{min}) to the marketed Depakote given up to 4 times/day. However, the products were not equivalent in the fasting state (the C_{min} of the ER was lower during fasting than the C_{min} of the DR), and the sponsor was issued a Not Approvable letter on 6/17/98. In particular, not only did the mean C_{min}'s fail the bioequivalence criteria, but in 2/14 subjects, the plasma level throughout the day in the ER phase was lower than the C_{min} for the DR product. This raised the question of the performance of the product itself. The sponsor, at that time, argued that we should accept that the products would be equivalent in the fed state, and that therefore the product should be labeled for use only with meals. We found this argument unpersuasive for a number of reasons, including the fact that, in these studies, the "fed" state meant the drug was taken with an FDA-standard high fat meal; we could not be sure that the products would always be equivalent in the face of the different foods actually eaten by patients (see my reviews of 4/22/98 and 6/11/98).

Since that time, we have had numerous interactions with the sponsor. Ultimately, the sponsor decided to attempt to demonstrate bioequivalence between the ER and DR products by increasing the dose of ER compared to DR. They performed 2 studies in the fasting state: 1) M00-232, in healthy volunteers, a cross-over study in which subjects received Depakote DR, 875 mg/day, given BID, Depakote ER, 1000 mg/day, given once a day, or Depakote DR, 1250 mg/day, given BID, and Depakote ER, 1500 mg/day, given once a day. 2) M01-274, in patients already receiving Depakote DR. In this study, patients were switched to a daily dose of Depakote ER that was 8-20% greater than their current DR dose. The maximum daily dose of DR in this study was 4250 mg, and the maximum daily dose of ER was 5000 mg. The results of these studies were submitted in a re-submission dated 6/26/02.

This re-submission has been reviewed by Dr. Phil Sheridan, medical officer (review dated 12/19/02), Dr. Vaneeta Tanden, Office of Clinical Pharmacology and Biopharmaceutics, (review dated 11/26/02), and Dr. John Feeney, Neurology Team Leader, (memo dated 12/19/02).

In Study 232, the bioequivalence criteria were met for AUC and Cmax; the ratio for the Cmin of ER/DR was 1.25, but the upper limit of the 90% CI fell outside the standard criterion (1.330). However, since the Cmin for the ER was greater than the Cmin for the DR, this is not problematic. In Study 274, the products were equivalent.

Because there was a question raised in the original studies about product performance, Dr. Feeney examined the time-concentration plots for individual patients in these studies. He notes that in Study 232, there was 1 subject of the 33-35 studied whose plasma level on the ER product was always lower than the Cmin of the DR. Similarly, in Study 274, there were 3 subjects of the 64 studied whose plasma levels on the ER product were always lower than the Cmin during DR treatment. The sponsor argues that this is technically true in only 2 subjects; in the other subjects, there are a few values on the ER formulation that are greater than the Cmin of the DR. Despite this, these 2 patients are quite close to meeting these "failure" criteria. The explanation for this is unclear. The sponsor attributed this outcome in the original studies to the possibility that some patients had an unusually rapid GI transit time, especially in the fasted state. Interestingly, there have been a number (about 20) of post-marketing reports of "intact" tablets in the stool; presumably about half of these patients had GI abnormalities. In these two new studies, the sponsor attributes this finding primarily to variability, and notes that there are several patients whose AUC on the ER was considerably greater than while on the DR.

Therefore, in the new studies, there appears to be a rate of between 1.5-5% of subjects/patients whose plasma levels during ER treatment are consistently lower than their levels during DR treatment. We have discussed this finding with several reviewers in OCPB, and there appears to be no generally accepted standard for assessing product performance in vivo beyond the application of the BE criteria; that is, if the BE criteria are met, individual time-concentration curves are ordinarily not examined. Presumably, if the BE criteria are met for a given treatment in a typical case, there may be a number of patients in whom the treatment being investigated performs consistently worse than the comparator; we simply have not been able to determine how often, if ever, this happens. This is particularly true for cases analogous to the case here; that is, when a demonstration of equivalence is attempted between an immediate release product and a modified release product.

Despite this finding, I believe that the application can be approved.

First, as is clear, the products, given the comparative dosing regimens, meet the pre-specified and standard criteria for equivalence. The fact that a small number of subjects/patients appears to have consistently lower plasma levels on ER compared to DR is of some concern, but may not be unusual. Further, the Agency at one time had employed a standard for bioequivalence referred to as the 75-75 rule; this rule required that there be no more than a 20% difference on Cmax and AUC between new product and reference, and that, in at least 75% of subjects, the bioavailability on the new product had to have been at least 75% of the reference product. While this rule no longer applies, it did allow for the possibility that 25% of patients would not meet the criteria (I believe that the actual degree of these individual "failures" was of no consequence, although, of course, if many patients failed by a great deal, overall equivalence would not be likely). In fact, both Dr. Uppoor and the sponsor have re-analyzed the two studies; both have found that the 75-75 rule is met in each study.

Although we have no definitive data about the expected rate of such failures in typical studies of this sort to guide us on this point, I find the ancillary analyses and the relatively low rate of such failures (between ———, reassuring.

For this reason, then, I conclude that the application can be Approved. It is worth noting that we have no data on the performance of the product in the pediatric population, in which there are at least theoretical concerns about its performance (pediatric patients may have more rapid GI transit times than adults). For this reason, the approval of this product for epilepsy will apply only to adults. I will issue, therefore, the attached Approval letter, with the appended labeling as agreed to with the sponsor.

Russell Katz, M.D.

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ON ORIGINAL**

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/s/

Russell Katz
12/20/02 08:00:23 AM
MEDICAL OFFICER

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MEMORANDUM

NDA 20-782

NDA 21-168/SLR-004 Depakote ER Tablets

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Conversion from Depakote to Depakote ER in Patients with Epilepsy

DATE: December 19, 2002

A new drug application for Depakote ER was received on June 17, 1997. The application provided for an extended-release formulation of divalproex sodium which would allow for once-a-day dosing regimen in contrast to the already marketed Depakote (divalproex delayed release tablets) which required dosing between 2 to 4 times per day. The original application for Depakote ER (NDA 20-782) contained no controlled trial data, but instead relied upon 2 bioequivalence studies between Depakote and Depakote ER.

On June 17, 1998, DNDP issued a Not Approvable letter for the application. Subsequently, the sponsor performed controlled trials in a different indication, migraine, and Depakote ER has been marketed under NDA 21-168. The current submission, therefore, represents a response to the Not Approvable letter and would provide a new indication for the already marketed drug product.

Bioequivalence Studies in the Original Application

Study M95-376 included 3 dose groups: ER fed, ER fasted, and DR fasted. For the fasted state, the AUCs were equivalent by the usual standard. The Cmax of the ER fasted was lower than the Cmax of DR fasted and failed equivalence standards. However, DNDP has previously accepted that valproate products given less frequently can be deemed equivalent to marketed products if only the AUCs are equivalent, while the Cmax is lower and the Cmin is greater. Therefore, the lower Cmax with ER fasted was not considered a problem.

The Cmin of ER fasted was not equivalent to DR fasted and was lower than Cmin of DR fasted, therefore failing the above division standard. The division also identified 2 patients whose plasma valproic acid levels after ER fasted remained lower *throughout the entire day* than the Cmin after DR fasted. This pattern of data suggested unacceptable product performance.

Study M95-401 included 2 dose groups of patients with epilepsy on another concurrent AED: DR fed and ER fed. In the fed state, the products were bioequivalent.

Overall, because of the failure of Cmin in the fasted state, Depakote was deemed to not meet the DNDP standard for a new valproate product given once daily.

Bioequivalence Studies in the Current Application

The current application contains the results of 2 bioequivalence studies. The designs of these studies were discussed in great detail by the sponsor and DNDP after the original Not Approvable letter was sent. The results have been reviewed by Drs. Veneeta Tandon and Ramana Uppoor in the Clinical Pharmacology/Biopharmaceutics Review. Dr. Sheridan has performed the primary clinical review.

M00-232 was a study in healthy volunteers comparing the bioequivalence of DR to ER at 2 different dose levels of DR and with an 8-20% higher total daily dose of ER than DR. The ER doses and the morning DR doses were given in the fasted state, while the other DR doses were given under modified fasting conditions. The 2 dose comparisons (in total daily dose) were: 1000mg ER vs 875mg DR and 1500mg ER vs 1250mg DR. For AUC and Cmax, both dose comparisons were within the usual equivalence standard. For Cmin, equivalence was demonstrated for the lower dose comparison. Using a 90% confidence interval, the Cmins for the 1500mg ER/1250mg DR comparison were not equivalent, but the Cmin for the ER product was higher than for the DR product, thereby meeting DNDP's standard for a new valproate product.

M01-274 was a study in patients with epilepsy taking concomitant AEDs. Patients taking Depakote DR tid were converted to Depakote ER at total daily doses 8-20% higher. The ER doses and the morning DR doses were given in the fasted state, while the other DR doses were given under modified fasting conditions.

Within the dose ranges studied in M01-274, AUC, Cmax, and Cmin all met the usual standards for equivalence. The experience with total daily doses of Depakote DR above 3000mg/day was limited to only 4 patients.

Performance of Depakote ER, as Measured by Outliers from the Four Above Bioequivalence Studies

As mentioned above, the Not Approvable letter identified 2 normal volunteers whose plasma valproic acid levels, when treated with ER fasted, were consistently lower throughout the day than the Cmin for DR fasted. This suggested poor product performance. In the more recent bioequivalence studies, with the daily dose of Depakote ER adjusted upward by 8-20%, Dr. Tandon has once again looked at performance outliers.

In M00-232, Dr. Tandon has described several subjects (Subjects 107,110) whose valproic acid concentrations are lower at all time points throughout the

day, while on ER vs DR at the higher dose comparison (1250mg DR/1500mg ER). Inspection of the data (p25 of her review) reveals that the concentrations are reasonably comparable for these subjects (Subjects 107,110) and, in fact, at the lower dose comparison (875mg DR/1000mg ER) the concentrations are superimposable at some time points during the day.

There is one subject (103) however, who only contributed data to the low dose comparison in the trial, and whose concentrations on ER throughout the day are always below the Cmin on DR (see p24 of Dr. Tandon's review). The Cmin on ER appears to be approximately half the Cmin on DR. This is the same outlier pattern described in the Not Approvable letter.

In M01-274, Dr. Tandon has described 6 patients whose Cmin on ER is less than half the Cmin on DR. The concentration vs time plots for these 6 patients are not included in Dr. Tandon's review, but Dr. Upoor has reviewed these. Three of the 6 appear (by visual inspection of the curves) to have concentrations on ER throughout the day which are always below the Cmin on DR (Subjects 105,132,and 809). The 6 low Cmin patients represented different dose groups and different concomitant AED groups.

Therefore, across both studies with a total of 100 subjects, there are 4 with this pattern. These 4 were the subject of internal discussions involving the clinical and biopharm groups. For Subject 105, assay samples were damaged during shipment, so an alternative explanation exists for this patient's results. The general view among reviewers for the other outliers is that this pattern represents the variability present with any new controlled release product, variability that is not usually investigated this fully. At one time a "75/75 rule" existed for determining bioequivalence. That rule required that the ratio of test to standard for a given parameter fall within 0.75-1.25 for at least 75% of subjects. Dr. Upoor determined that the Cmin for Depakote ER met that criterion for the M01-274 study. Therefore, I do not believe there is evidence for any systematic product failure in these studies.

Inspections

The inspections of several sites from Study M01-274 have been completed. Several small concerns were raised, but were not felt to be clinically important.

The final inspection report for new manufacturing sites is also finalized and is acceptable.

Labeling

Anticipating approval of the application, several issues have been addressed for labeling.

First, as described above, there is little experience in the new bioequivalence studies at doses greater than 3000mg/day of Depakote DR. Therefore, it seems appropriate to restrict the labeling to the dose range studied.

Second, the age range of patients studied does not represent pediatric populations. Therefore, it seems appropriate to restrict labeling to the age range studied.

Postmarketing Reports

The sponsor has provided a review of postmarketing reports of Depakote ER tablets appearing in the stool. There have been 19 such reports. No serious adverse events resulted. The sponsor believes that, because this extended release product is absorbed across the entire GI tract, conditions such as colectomy or irritable bowel syndrome may cause rapid GI transit and result in tablets in the stool. Proposed labeling will describe this phenomenon.

Name Confusion

During a meeting with the sponsor on May 3, 2001, several reports relating to dispensing and/or prescribing errors due to Depakote and Depakote ER name confusion were discussed. The sponsor has subsequently changed the carton and container labeling, but the effectiveness of this maneuver in reducing confusion is not addressed in the current submission. Further discussion of this issue will be needed in the future but need not impact the action on the current submission.

Comments

The sponsor has provided data showing that adult patients, within the dose range studied, can be converted from Depakote DR to Depakote ER with reliable and acceptable performance. Therefore, an Approval action is appropriate with the labeling language mutually agreed upon by the sponsor and DNDP.

There are 3 issues that will merit continued attention. First, name confusion in the writing and dispensing of Depakote and Depakote ER needs to be periodically re-evaluated and appropriate corrective actions taken. Second, the reporting of Depakote ER tablets in the stool through postmarketing surveillance needs to be followed. Third, the sponsor has been encouraged to evaluate Depakote ER in pediatric patients.

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/s/

John Feeney
12/19/02 04:38:48 PM
MEDICAL OFFICER

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