CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-168

Clinical Pharmacology and Biopharmaceutics Review

NDA 21-168
Depakote® ER tablets

JUL 2 4 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Divalproex sodium (Depakote® ER)
500 mg extended release tablet
NDA 21-168

Abbott Laboratories,
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

Submission Dates: September 30, 1999, July 14, 2000
Reviewer: Maria Sunzel, Ph.D.
Indication: Migraine prophylaxis
Submission Type: Original NDA

INTRODUCTION

Background:

Depakote® is currently approved for treatment of migraine prophylaxis, epilepsy and mania. The approved pharmaceutical formulations for these indications are sprinkle capsules (125 mg) and delayed-release tablets (125, 250, 500 mg) given as divided daily doses. The dosing recommendations for migraine prophylaxis are 500-1000 mg/day divided into twice-daily doses.

The currently submitted NDA concern an extended release (Depakote® ER) formulation, intended for once daily dosing. This formulation was not approved for treatment of epilepsy, because of the equivalence was not established for C_{min}, with the marketed delayed-release formulation as a reference (NDA 20-782, non-approvable letter 1998). The ER formulation exhibited lower trough concentrations at the end of a dosing interval and since no clinical studies were submitted for NDA 20-782, seizure control during Depakote® ER monotherapy treatment could not be assured. The clinical pharmacology and biopharmaceutics (CPB) review of NDA 20-782 is dated 4/10/98, with a NDA amendment review dated 6/2/98, and was performed by Rae Yuan, Ph.D. The submission for NDA 20-782 contained eight pharmacokinetic/biopharmaceutic studies.

The NDA 21-168 contains:

- One pharmacokinetic study evaluating the influence of meals with different caloric content on the bioavailability of the new ER formulation with the marketed delayed release formulation as reference
- A revised dissolution specification utilizing IVIVC. The original specifications were submitted in NDA 20-782, and were found to be unacceptably wide by the previous reviewer.

The following questions were considered in this review:

- Does meals of different composition influence the pharmacokinetics of valproate favorably when co-administered with the new ER formulation?
- Are the revised dissolution specifications adequate?
- Is the sponsor's labeling acceptable?

The current NDA cross-references NDA 20-782 for studies regarding bioequivalence, concomitant anti-epileptic drug therapy and food effects. For evaluations of the cross-referenced studies please refer to the CPB reviews of NDA 20-782, dated 4/10/98 and 6/2/98.

The clinical section of the current NDA includes a migraine prophylaxis study where the effectiveness of the new ER formulation was evaluated in 122 patients with a history of migraine headaches.

TABLE OF CONTENTS

APPEARS THIS WAY
ON ORIGINAL

Study #1. Study M98-924: Bioavailability of valproate from an extended-release (ER) tablet formulation of divalproex sodium relative to that of a conventional delayed release (DR) tablet formulation under different nonfasting regimens

(NDA 21-168 volumes 1.12-16)

Background

Food intake delays the time to peak concentration by 4 h for the approved delayed release (DR) tablet formulation. However, no special dosing recommendations regarding timing of meals are given in the label since the influence on the pharmacokinetics was considered to be minor. In an earlier reviewed study (NDA 20-782, Study M 95-376) repeated doses of the current ER formulation was given with or without a standardized breakfast, and the DR formulation (fasting) as a reference. The standardized breakfast content was 664 kcal, 43% fat content, which is somewhat lower than the recommended 1000-kcal 'FDA-breakfast'. The ER tablet performed sub-optimally compared to the DR tablet, and performed somewhat better when administered concomitantly with food, especially with respect to C_{min}. The trough concentrations are judged to be important for adequate seizure control, particularly during Depakote mono-therapy. The sponsor performed one additional study described below, to determine if the ER tablet performs adequately compared to the DR tablet, when administered with food varying in fat and protein content.

Study Design

An open label, randomized, single center, 5-way crossover design was chosen for this repeated dose study in healthy volunteers. The subjects received 1000 mg divalproex sodium per day, during eight consecutive days. Plasma samples, for pharmacokinetic evaluation, were collected before a.m. dose intake on Days 6-8, and frequently during the last day of dosing. The subjects received the following regimens:

A. 1000 (2x500) mg ER tablets (test), q.d., a.m. after a 13-h fasting period
B. 1000 (2x500) mg ER tablets (test), q.d., a.m. immediately prior to a 300 kcal breakfast
C. 1000 (2x500) mg ER tablets (test), q.d., a.m. immediately prior to a 600 kcal breakfast
D. 1000 (2x500) mg DR tablets (reference), b.i.d., a.m. & p.m. dosing, immediately prior to a 300 kcal breakfast, and a 900 kcal dinner
E. 1000 (2x500) mg DR tablets (reference), b.i.d., a.m. & p.m. dosing, immediately prior to a 600 kcal breakfast, and a 750 kcal dinner

The content of the dinners served during regimens B and C corresponded to the content of the dinners served during regimens D and E, respectively.

Thirty-eight subjects (20-52 yrs, 34 M/4 F) were enrolled, and 33 subjects completed the study. Six of these subjects had previously participated in earlier studies with Depakote® ER, where it was observed that they had lower bioavailability than other volunteers that took part in the same studies. These individuals were included in the study to test the hypothesis that they had a faster GI transit times than the average subject, resulting in incomplete absorption and lower relative bioavailability compared to the DR formulation.

Pharmacokinetic Analysis

Observed values were used for determination of maximum plasma concentrations (C_{max}), the time to C_{max} (t_{max}), and the minimum plasma concentrations (C_{min}). If the C_{max} occurred after the second dose intake of the DR formulation (regimens D and E) the t_{max} was related to the time of the second dose intake during Day 8. The AUC_{0-24h} was calculated by the linear trapezoidal method. The fluctuation index (DFL) was calculated over the last 24-h period ($DFL=(C_{max}-C_{min})/C_{average}$). The parameters were tested for effects of sequence, period and regimen (F-test). The parameters of the different dosing regimens were compared by the means of repeated measure analyses.

Bioanalytical Method

Plasma concentrations of valproic acid (VPA) were determined by ——— ——— The lower limit of quantitation of VPA in human plasma was — µg/mL. Calibration curves were constructed in the plasma concentration range of ——— µg/mL (inter-assay precision — %; inter-assay accuracy — — %). Samples quantified above the highest standard, were diluted and reanalyzed. The inter-day precision of the quality controls was — % or less, with a recovery of ——— %.

Results

The plasma concentration-time curves during the last day of dosing, Day 8 are shown in Figure 1. The reference formulation, the DR tablet administered twice daily immediately prior to a meal, gave consistently higher plasma concentrations compared to the test formulation, the ER tablet, administered once daily with or without meals.

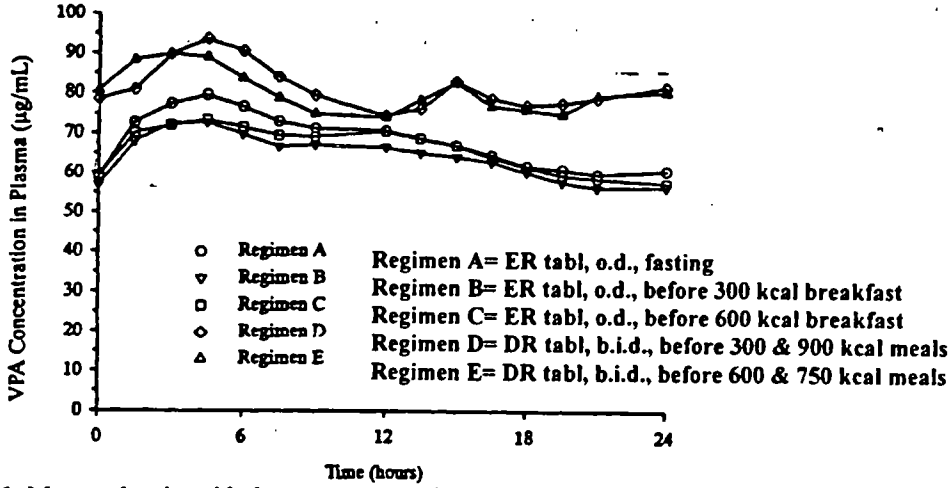

Figure 1. Mean valproic acid plasma concentration-time curves on Day 8 after once (Regimens A, B, C) or twice (Regimens D, E) daily doses of 1000 mg Depakote® as ER (test) and DR (reference) tablets.

The pharmacokinetic parameters after the different treatments are shown in Table 1.

Table 1. Pharmacokinetic parameters (mean ± SD) on Day 8 after once (Regimens A, B, C) or twice (Regimens D, E) daily doses of 1000 (2 x 500) mg Depakote® as ER and DR tablets.

Pharmacokinetic Parameters	Regimens				
	A: Test Fasting ER N=34	B: Test 300 kcal ER N=32	C: Test 600 kcal ER N=34	D: Reference 300 kcal DR N=35	E: Reference 600 kcal DR N=34
T_{max} (h)	6.6 ± 5.3	9.1 ± 7.2	8.1 ± 6.4	4.1 ± 2.6	4.2 ± 3.1
C_{max} (µg/mL)	82.6 ± 18.0	78.0 ± 18.6	79.4 ± 15.1	107.2 ± 14.6	106.4 ± 14.9
C_{min} (µg/mL)	52.0 ± 18.3	48.3 ± 20.1	51.1 ± 16.5	61.1 ± 10.9	60.9 ± 13.7
AUC_{0-24} (µg*h/mL)	1658 ± 425	1547 ± 448	1595 ± 354	1951 ± 276	1926 ± 311
C_{avg} (µg/mL)	69.1 ± 17.7	64.5 ± 18.6	66.5 ± 14.7	81.3 ± 11.5	80.3 ± 12.9
DFL	0.48 ± 0.22	0.51 ± 0.24	0.45 ± 0.22	0.57 ± 0.11	0.58 ± 0.15

All once-daily dose regimens with the ER formulation (test) gave approximately 20% lower AUC_{0-24h} values at steady state, compared to the twice daily dose regimens with the DR formulation (reference). The formulations were not bioequivalent, as shown in Table 2.

Table 2. Point estimates and 90% confidence intervals of AUC_{0-24h} Day 8 after once (Regimens A, B, C) or twice (Regimens D, E) daily doses of 1000 (2 x 500) mg Depakote® as ER and DR tablets.

Regimens Test *vs.* Reference	Relative Bioavailability (AUC_{0-24h}) Point Estimate*	90% Confidence Interval
A (ER fasting) *vs.* D (DR 300 kcal)	0.833	0.763 – 0.909
B (ER 300 kcal) *vs.* D (DR 300 kcal)	0.766	0.703 – 0.834
C (ER 600 kcal) *vs.* E (DR 600 kcal)	0.815	0.767 - 0.865
ABC *vs.* DE#	0.806	0.755 - 0.860

*Antilogarithm of the difference (test – reference) of the least squares means for the logarithms
#Composite of the three ER regimens or the two RD regimens

A similar trend of lower values was observed for C_{max} and C_{min} when the test formulations were compared to the reference formulations, as shown in Table 3.

Table 3. Point estimates and 95% confidence intervals on Day 8 after once (Regimens A, B, C) or twice (Regimens D, E) daily doses of 1000 (2 x 500) mg Depakote® as ER and DR tablets. Left panel: C_{max}. Right panel: C_{min} NB. C_{min} values were not log-transformed, due to skewedness in the data.

Results for C_{max}

Regimens Test vs. Reference	Relative Bioavailability Point Estimate*	95% Upper Confidence Bound
A vs. D	0.765	0.818
B vs. D	0.712	0.761
C vs. E	0.739	0.786
ABC vs. DE▼	0.739	0.779

* Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
▼ Composite of the three ER regimens or the two DR regimens.

Results for C_{min}

Regimens Test vs. Reference	Relative Bioavailability Estimate of Ratio of Means	95% Lower Confidence Bound
A vs. D	0.862	0.770
B vs. D	0.783	0.692
C vs. E	0.829	0.754
ABC vs. DE▼	0.824	0.752

▼ Average of the three ER regimens or the two DR regimens.

The degree of fluctuation was statistically significantly lower for the ER formulations, where the p-values for regimens A (ER, fasting) and B (ER, 300 kcal) *vs.* regimen D (DR, 300 kcal) were 0.0087 and 0.0487, respectively. The corresponding p-value of regimen C (ER, 600 kcal) vs. regimen E (DR, 600 kcal) was 0.0006. Since the peak concentrations were significantly lower, and would not reach bioequivalence to the DR formulation, a lower DFL would be expected.

The subjects with previously documented suboptimal delivery of VPA from the ER formulation were not distinguishable from the remainder of the studied subjects. The sponsor hypothesizes that gastrointestinal transit time is highly variable, and not consistent within one individual at different occasions.

In conclusion, the new ER formulation did not show bioequivalence to the approved DR formulation with respect to AUC, C_{max} or C_{min}. Although 90% confidence intervals were not constructed for the latter two parameters by the sponsor, non-equivalence can be determined from the point estimates of C_{max} and lower boundaries of C_{min}.

Study # 2. Dissolution specifications (revised from original specifications of NDA 20-782)

(NDA 21-168: vol. 1.16; NDA 20-782: vols. 1.6 (Study 96/603), 1.7 (Studies 96/592, /96/425), 1.13, 1.16)

In vitro dissolution method

The pharmaceutical formulation that has been developed for oral once-daily administration is a hydrophilic matrix tablet of divalproex sodium.

The compound itself is stable, and contains equimolar proportions of sodium valproate and valproic acid. Divalproex sodium has a high aqueous solubility a neutral pH (36 mg/mL at pH 6.17) with lower solubility at pH below its pKa of 4.8 (2 mg/mL at pH 4.7).

An initial *in vitro* dissolution method was found to result in release rates that were slower than the observed *in vivo* absorption. A new method was developed to generate *in vitro* release profiles of the formulations that are predictive of their *in vivo* performance. Both paddle speed and media with different pH (0.1 N HCl at 100 rpm, water at 100 rpm, 0.05 M phosphate buffer pH 7.5 at 50 rpm) were tested, as shown in Figure 2. The dissolution method described below was found to be superior to the other media mainly due to the effect of SDS on the polymer.

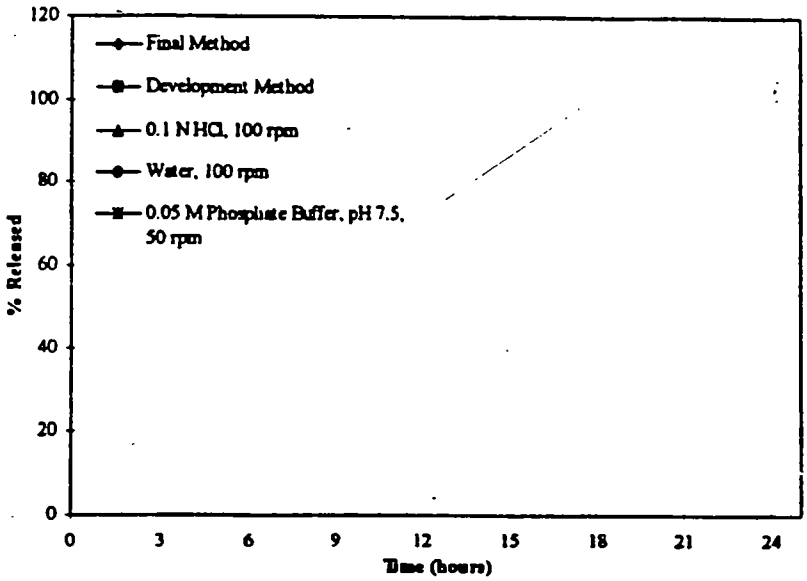

Figure 2. Drug release media comparison for 500 mg divalproex sodium ER tablets (NDA 20-782, vol. 1.6, p. 226).

In addition, a series of studies with factorial design were conducted where the influence of agitation intensity (paddle speeds of 50, 75, 100 rpm), apparatus (USP 1 or 2), pH, ionic strength of the dissolution medium and sodium dodecyl sulfate (surfactant) concentration were investigated. Optimal conditions were chosen. The proposed method was shown to be predictive of *in vivo* absorption (NDA 20-782, vol. 1.7, Study 96/592).

The proposed *in vitro* dissolution method is:

Apparatus:	USP Apparatus 2 (paddle), 100 rpm
Acid medium:	0.1 N HCl, 500 mL, 37±0.5°C for 45 min
Drug release medium:	0.05M phosphate buffer with 75 mM sodium dodecyl sulfate (SDS), pH 5.5, 900 mL, 37±0.5°C

In vitro dissolution specification

In the previous NDA review (20-782), using the *in vitro-in vivo* correlation (IVIVC), it was estimated that the difference in the concentrations predicted from the lower and upper boundaries of the dissolution specifications proposed by the sponsor was more than 20%. The sponsor has revised the dissolution specification to the following limits;

Proposed dissolution specifications (% released)

Time (h)	Lower limit	Upper limit	Purpose/Comment
3			Confirm no dose dumping
9			Ensure controlled release
12			Ensure controlled release
18			Confirm controlled release

The limits have been changed from the earlier submission (NDA 20-782) where the limits were 3 h: — 9 h: — 12 h: — and 18 h: —

Justification of the *in vitro* dissolution specification by IVIVC

The sponsor has justified the proposed *in vitro* dissolution specification by an IVIVC, which has been slightly modified from the previously submitted IVIVC (NDA 20-782, vols. 1.7, 1.16). The IVIVC is based on an *in vivo* study (M95-414, NDA 20-782), where three ER formulations with different release properties (slow, to-be-marketed, and fast) were used for the internal validation. The previously reviewed data for *in vitro* dissolution and *in vivo* performance has been re-analyzed — and the proposed dissolution specifications are based on that analysis.

The following models were used for the IVIVC:

Previous model (NDA 20-782): % absorbed drug = 8.79 + 0.90 x % dissolved drug

Adjusted model (current NDA): Absorption rate = Intercept + 0.90 x dissolution rate; where the intercept = 0.08 x dose/3 (0-3 h after drug intake; 0.08 = 8.00%) and the intercept = 0 (at all time points greater than 3 h)

The sponsor provided the upper and lower boundaries for the predicted *in vivo* parameters, as shown in Table 4.

Table 4. Predicted *in vivo* parameters for the lower and upper dissolution specifications.

Parameter	Lower limit	Upper limit	Ratio (lower/upper limit)
C_{max} (µg/mL)			
t_{max} (h)			
AUC (µg x h/mL)			
F %*			

* Absolute bioavailability

From the ratios (lower/upper limits) in Table 4, the sponsor has calculated a maximal difference of 18.3%, and 7.9% for C_{max} and AUC, respectively. The corresponding observed values *in vivo* (Study M95-414) for the to-be-marketed formulation of C_{max} and AUC were — µg/mL and — µg x h/mL, respectively.

This reviewer recalculated the IVIVC using a deconvolution approach, based on *in vitro* dissolution data and deconvolution from *in vivo* absorption data (model: % absorbed drug = 9.03 + 0.895 x % dissolved drug). A sigmoid E_{max} model (WinNonlin Professional, version 3.0) was

fitted to the dissolution data. The first derivative of the fitted model was used as the dissolution rates that were convolved by use of the pharmacokinetic disposition parameters given in Study M95-414 for the prediction of the plasma VPA concentration-time data (NDA 20-782; i.v. infusion, 1-compartment model).

The mean prediction errors (%PE) for the internal validation for both C_{max} and AUC were less than 10%, as shown in Table 5 (reviewer's analysis).

Table 5. Internal predictability of the IVIVC (reviewer's analysis)

Parameter	Release Profile (Study 95-414, NDA 20-782)	Observed*	Predicted	% PE†
C_{max}* (mg/L)	Slower	28.76		
	To-be-marketed	27.44		
	Faster	36.36		
			mean	7.43**
AUC_{0-72h}* (mg.h/L)	Slower	965.8		
	To-be-marketed	985.4		
	Faster	1080.2		
			mean	7.85**

* Observed C_{max} and AUC values determined from the mean plasma concentration-time curves (not mean of individual C_{max} and AUC)
† % Prediction error (% PE) = [(observed value-predicted value)/ observed value] x 100
** based on absolute values of %PE

The reviewer's model was also applied to assess the upper and lower boundaries of the dissolution specifications of the current NDA. The lower and upper limits (% difference from the estimated C_{max} of the to-be marketed formulation) for C_{max} were and mg/L, respectively. The corresponding % differences for AUC_{0-72h} were - respectively. The predicted VPA plasma concentration – time curves are depicted in Figure 3.

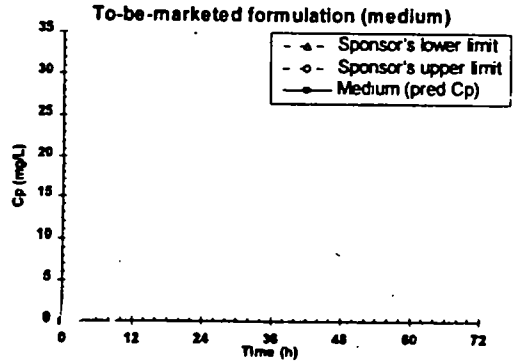

Figure 3. Predicted VPA plasma concentration – time curves of the to-be-marketed ER formulation (solid line) using reviewer's IVIVC estimations. Dashed concentration – time curves indicate upper and lower limits of the proposed dissolution specifications.

Upon request, the sponsor provided the prediction errors for the different ER formulations (C_{max} and AUC) using the proposed, adjusted IVIVC model. The sponsor's mean prediction errors for the internal validation for both C_{max} and AUC were less than 10%, using the IVIVC model supplied in NDA 21-168, as shown in Table 6.

Table 6. Internal predictability of the IVIVC (sponsor's analysis)

Parameter	Release Profile (Protocol 95-414, NDA 20-782)	Observed*	Predicted	% PE†	% PE††
C_{max}* (mg/L)	Slower	/			5.5
	To-be-marketed				-10.3
	Faster				-2.1
			mean	5.83**	5.97**
$AUC_{0-\infty}$* (mg.h/L)	Slower	/			9.5
	To-be-marketed				7.9
	Faster				7.1
			mean	3.35**	8.16**

*C_{max} and AUC values determined from the individual plasma concentration-time curves
† % Prediction error (PE) = [(observed value-predicted value)/ observed value] x 100
†† Prediction errors for C_{max} and AUC based on values calculated from the mean plasma concentration-time curves (determined by reviewer)
** based on absolute values of %PE

The internal validation is acceptable as a Type A correlation where both C_{max} and AUC estimations give a prediction error less that 10% (*Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997).*

The sponsor's IVIVC method yields estimates for AUC and C_{max} that are within acceptance limits. This indicates that the dissolution specifications proposed by the sponsor are appropriate, and will ensure that different batches are comparable from a bioequivalence point of view. Therefore, the proposed dissolution specifications (NDA 21-168) are recommended, as described in the Comments section, Study #2.

APPEARS THIS WAY

COMMENTS

Study #1 (Study Report M 98-924):

The new ER formulation did not show bioequivalence to the approved DR formulation with respect to AUC, C_{max} or C_{min}. Although 90% confidence intervals were not constructed for the latter two parameters by the sponsor, non-equivalence can be determined from the point estimates of C_{max} and lower boundaries of C_{min}.

The study design is comprehensive, where the effect of meals with different caloric content was investigated after administration of the two different formulations. The pharmacokinetics of VPA was investigated after repeated doses, which may obscure differences, since a steady state design is less sensitive in detecting differences between treatments, compared to single doses. However, the results may be confounded due to the fact that the study medications were given immediately prior to the meals with different composition. This precludes a clear picture of the potential food effect since mixed effects of food intake and each individual's phase of gastric emptying (i.e. migrating myoelectric complexes) that the dosage form hits may influence the results. The consistent performance of both formulations irrespective of food content may indicate that absorption was similar to the fasting state in most cases. In the previously submitted repeated dosing study (NDA 20-782, Study M 95-376), the ER tablet performed slightly better when it was administered immediately after breakfast (664 kcal) compared to the DR formulation taken in the fasting state.

The ER formulation is not bioequivalent to the DR formulation. The positive clinical results of Depakote ER in migraine prophylaxis may be a result of that this effect is achieved at lower VPA plasma concentrations than those needed for the treatments of epilepsy and mania.

Thus, this study just supports the availability of bioavailability information on the ER product in healthy volunteers. Since the ER tablet is being indicated for prophylaxis of migraine, similar pharmacokinetics would be anticipated in patients when they are not having an acute migraine attack. The study clearly demonstrates that this product should not be substituted for the DR product for epilepsy patients or patients treated for mania on the basis of pharmacokinetic information.

Study #2 (Dissolution specifications):

The sponsor's proposed *in vitro* dissolution method is acceptable, as described below;

Apparatus:	USP Apparatus 2 (paddle), 100 rpm
Acid medium:	0.1 N HCl, 500 mL, 37±0.5°C for 45 min
Drug release medium:	0.05M phosphate buffer with 75 mM sodium dodecyl sulfate (SDS), pH 5.5, 900 mL, 37±0.5°C

A Type A *in vitro–in vivo* correlation has been established. The sponsor's proposed dissolution specifications, are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics, as described below:

Dissolution specifications (% released)

Time (h)	Lower limit	Upper limit	Purpose/Comment
3			Confirm no dose dumping
9			Ensure controlled release
12			Ensure controlled release
18			Confirm controlled release

The Type A *in vitro–in vivo* correlation may be used for waivers for *in vivo* bioequivalence studies of future manufacturing changes or new formulations according to *Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997.*

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

RECOMMENDATION

From a pharmacokinetic point of view, this NDA for migraine prophylaxis is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Type A *in vitro–in vivo* correlation and the sponsor's proposed dissolution specifications, as outlined in the comments, are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The Type A *in vitro–in vivo* correlation may be used for waivers for *in vivo* bioequivalence studies of future manufacturing changes or new formulations according to *Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997.*

The sponsor is requested to incorporate all labeling changes.

Please forward the comments and the labeling changes to the sponsor.

Maria Sunzel, Ph.D., /S/ 7/24/00

RD/FT initialed by Chandra Sahajwalla, Ph.D., /S/ 7/24/00

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: July 10, 2000; Attendees: Drs. Armando Oliva, Mehul Mehta, Chandra Sahajwalla, Ray Baweja, Jerry Fetterly and Maria Sunzel

c.c.: NDA 21-168, HFD-120, HFD-860 (Mehta, Sahajwalla, Sunzel, Baweja), HFD-340 (Viswanathan), CDR (Biopharm) and FOI files (HFD-19)

Redacted 4

pages of trade

secret and/or

confidential

commercial

information