CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-593/S-006

Trade Name: Depacon

Generic Name: Valproate sodium injection

Sponsor: Abbott Laboratories

Approval Date: 01/24/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-593/S-006

Abbott Laboratories
Attention: Steven E. Townsend
Associate Director, PPD Regulatory Affairs
100 Abbott Park Road
D-491/AP6B-1
Abbott Park, Illinois 60064-6108

Dear Mr. Townsend:

Please refer to your supplemental new drug application dated June 30, 2000, received July 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depacon® (valproate sodium injection).

We acknowledge receipt of your submissions dated July 24, 2001 and November 20, 2001. Your submission of July 24, 2001 constituted a complete response to our May 3, 2001 action letter.

This supplemental new drug application proposes an increased rate of infusion for Depacon® (valproate sodium injection).

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). We note that you have indicated your agreement with the attached labeling in an email on January 18, 2002 to Dr. Ware of this Division.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-593/S-006." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
1/24/02 02:23:27 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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Abbott Laboratories
Attention: Steven E. Townsend
100 Abbott Park Road
D-491/AP6B-1
Abbott Park, IL 60064-6108

Dear Mr. Townsend:

Please refer to your supplemental new drug application dated June 30, 2000, received July 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depacon® (valproate sodium injection).

We acknowledge receipt of your submissions dated:

September 15, 2000	January 19, 2001
November 14, 2000	April 12, 2001

This supplemental new drug application proposes an increased rate of infusion for Depacon.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling identical to the attached proposed labeling.

We have the following comments about the major proposals you have made for the various sections of labeling:

Dosage and Administration

As you know, your submission did not include direct measurements of free valproate levels at Cmax. Simulations suggest that at Cmax, levels of free valproate at these greater infusion rates are about 50% higher than those at Cmax seen after the approved 60 minute infusion. [ ]

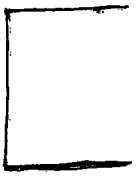
As you know, the 60 minute infusion rate is approved because, at that rate, Depacon is bioequivalent to oral valproic acid. As such, we can reliably conclude that this rate can be given safely, because it is based on the safety of the oral product, which is well documented. [ ]

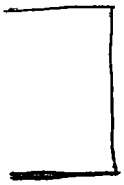
[ ]

[ ]. We do believe, however, that the data support a statement describing the experience with these greater rates/doses in patients with low or undetectable levels of valproate, and we have proposed such a statement.

Clinical Pharmacology

Adverse Reactions





For these reasons, we believe the simple statement we have proposed which describes the ADRs seen in Study M98-398 is appropriate and sufficient.

All previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

We note from the inspection report by our Division of Scientific Investigations concerning Dr. Ramsay's site at University of Miami that his site administered the protocol infusions by manual push rather than by an infusion pump. We question whether a constant rate of infusion could be achieved without the use of an infusion pump. Please document how the infusions were given at the 12 other participating sites that enrolled patients for this study.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this/these change(s) prior to approval of this supplemental application.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

(No. 1564)

CN58-6072-R4-Rev. June, 2000

DEPACON®
VALPROATE SODIUM INJECTION

R_x only

BOX WARNING:
HEPATOTOXICITY:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPACON IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

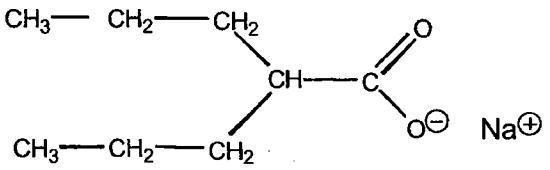
TERATOGENICITY:
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF VALPROATE PRODUCTS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS.

PANCREATITIS:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See **WARNINGS** and **PRECAUTIONS**.)

DESCRIPTION

Valproate sodium is the sodium salt of valproic acid designated as sodium 2-propylpentanoate. Valproate sodium has the following structure:



Valproate sodium has a molecular weight of 166.2. It occurs as an essentially white and odorless, crystalline, deliquescent powder.

DEPACON solution is available in 5 mL single-dose vials for intravenous injection. Each mL contains valproate sodium equivalent to 100 mg valproic acid, edetate disodium 0.40 mg, and water for injection to volume. The pH is adjusted to 7.6 with sodium hydroxide and/or hydrochloric acid. The solution is clear and colorless.

CLINICAL PHARMACOLOGY

DEPACON exists as the valproate ion in the blood. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics

Bioavailability

Equivalent doses of intravenous (IV) valproate and oral valproate products are expected to result in equivalent C_{max}, C_{min}, and total systemic exposure to the valproate ion when the IV valproate is administered as a 60 minute infusion. However, the rate of valproate ion absorption may vary with the formulation used. These differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

Administration of DEPAKOTE (divalproex sodium) tablets and IV valproate (given as a one hour infusion), 250 mg every 6 hours for 4 days to 18 healthy male volunteers resulted in equivalent AUC, C_{max}, C_{min} at steady state, as well as after the first dose. The T_{max} after IV DEPACON occurs at the end of the one hour infusion, while the T_{max} after oral dosing with DEPAKOTE occurs at approximately 4 hours. Because the kinetics of unbound valproate are linear, bioequivalence between DEPACON and DEPAKOTE up to the maximum recommended dose of 60 mg/kg/day can be assumed. The AUC and C_{max} resulting from administration of IV valproate 500 mg as a single one hour infusion and a single 500 mg dose of DEPAKENE syrup to 17 healthy male volunteers were also equivalent.

Patients maintained on valproic acid doses of 750 mg to 4250 mg daily (given in divided doses every 6 hours) as oral DEPAKOTE (divalproex sodium) alone (n=24) or with another stabilized antiepileptic drug [carbamazepine (n=15), phenytoin (n=11), or phenobarbital (n=1)], showed comparable plasma levels for valproic acid when switching from oral DEPAKOTE to IV valproate (1-hour infusion).

Eleven healthy volunteers were[redacted] single infusions of 1000mg IV valproate over 5, 10, 30, and 60 minutes in a 4-period crossover study. Total valproate concentrations were measured; unbound concentrations were not measured. After the 5 minute infusions, mean Cmax was 145 ± 32 µg/mL, while after the 60 minute infusions, mean Cmax was 115 ± 8

µg/mL. Ninety to 120 minutes after infusion initiation, total valproate concentrations were similar for all 4 rates of infusion. Because protein binding is nonlinear at higher total [redacted] concentrations, the corresponding increase in unbound Cmax at faster infusion rates will be greater.

Distribution
Protein Binding:
The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 µg/mL to 18.5% at 130 µg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See **PRECAUTIONS, Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution:
Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean terminal half-life for valproate monotherapy after an intravenous infusion of 1000 mg was 16 ± 3.0 hours.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations
Effect of Age:
Neonates - Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to

decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children - Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly - The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See **DOSAGE AND ADMINISTRATION**).

Effect of Gender:
There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).

Effect of Race:
The effects of race on the kinetics of valproate have not been studied.

Effect of Disease:
Liver Disease - (See **BOXED WARNING, CONTRAINDICATIONS,** and **WARNINGS**). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease - A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy:
The therapeutic range in epilepsy is commonly considered to be 50 to 100 μg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Equivalent doses of DEPACON and DEPAKOTE (divalproex sodium) yield equivalent plasma levels of the valproate ion (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Clinical Studies
The studies described in the following section were conducted with oral divalproex sodium products.

Epilepsy
The efficacy of DEPAKOTE (divalproex sodium) in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

In one, multiclinic, placebo controlled study employing an add-on design (adjunctive therapy), 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

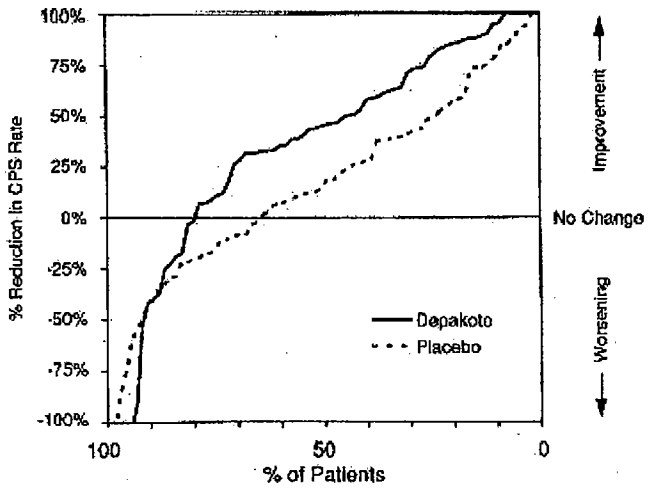
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at $p \leq 0.05$ level.

Figure 1 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a $\geq$ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 1



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 μg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

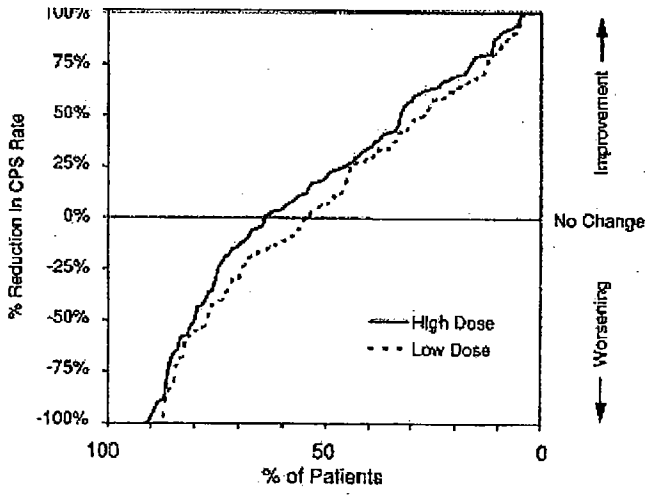
Monotherapy Study
Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose DEPAKOTE	131	13.2	10.7*
Low dose DEPAKOTE	134	14.2	13.8

*Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose DEPAKOTE.

Figure 2



INDICATIONS AND USAGE

DEPACON is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

DEPACON is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPACON is also indicated for use as sole and adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE **WARNINGS** FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION

CONTRAINDICATIONS

VALPROATE SODIUM INJECTION SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Valproate sodium injection is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months of valproate therapy. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering valproate products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPACON is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Use of DEPACON has not been studied in children below the age of 2 years. Above this age group, experience with valproate products in epilepsy has indicated that the

incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see **BOXED WARNING**).

Somnolence in the Elderly

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**).

Thrombocytopenia

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see **PRECAUTIONS**]) may be dose-related. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Post-traumatic Seizures

A study was conducted to evaluate the effect of IV valproate in the prevention of post-traumatic seizures in patients with acute head injuries. Patients were randomly assigned to receive either IV valproate given for one week (followed by oral valproate products for either one or six months per random treatment assignment) or IV phenytoin given for one week (followed by placebo). In this study, the incidence of death was found to be higher in the two groups assigned to valproate treatment compared to the rate in those assigned to the IV phenytoin treatment group (13% vs 8.5%, respectively). Many of these patients were critically ill with multiple and/or severe injuries, and evaluation of the causes of death did not suggest any specific drug-related causation. Further, in the absence of a concurrent placebo control during the initial week of intravenous therapy, it is impossible to determine if the mortality rate in the patients treated with valproate was greater or less than that expected in a similar group not treated with valproate, or whether the rate seen in the IV phenytoin treated patients was lower than would be expected. Nonetheless, until further information is available, it seems prudent not to use DEPACON in patients with acute head trauma for the prophylaxis of post-traumatic seizures.

Usage In Pregnancy

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPSY DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPSY DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (E.G., CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPSY DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE

EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 μg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 μg/mL or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 μg/mL (2.8 times the upper limit of the human therapeutic range).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepilepsy drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction
See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**

Pancreatitis
See **BOXED WARNING** and **WARNINGS.**

General
Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPACON be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE (divalproex sodium) as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPACON therapy should be modified or discontinued.

Since DEPACON may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See **PRECAUTIONS - Drug Interactions**).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Information for Patients
Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Since DEPACON may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed:

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Felbamate - A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 μg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 μg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:
Antacids - A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine - A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyl transferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed:
Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10,11-Epoxide - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam - The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam - Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with

other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine - In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate.

Phenobarbital - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin - Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin - In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproate therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

<u>Drugs for which either no interaction or a likely clinically unimportant interaction has been observed</u>:

Acetaminophen - Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine - In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium - Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam - Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids - Administration of a single-dose of ethinyloestradiol (50 μg)/levonorgestrel (250 μg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy

Pregnancy Category D: See **WARNINGS.**

Nursing Mothers

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when valproate is administered to a nursing woman.

Pediatric Use

Experience with oral valproate has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see **BOXED WARNING**). The safety of DEPACON has not been studied in individuals below the age of 2 years. If a decision is made to use DEPACON in this age group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

No unique safety concerns were identified in the 35 patients age 2 to 17 years who received DEPACON in clinical trials.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see **WARNINGS–Somnolence in the Elderly**). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**)

No unique safety concerns were identified in the 21 patients > 65 years of age receiving DEPACON in clinical trials.

ADVERSE REACTIONS

The adverse events that can result from DEPACON use include all of those associated with oral forms of valproate. The following describes experience specifically with DEPACON. DEPACON has been generally well tolerated in clinical trials involving 111 healthy adult male volunteers and 352 patients with epilepsy, given at doses of 125 to

6000 mg (total daily dose). A total of 2% of patients discontinued treatment with DEPACON due to adverse events. The most common adverse events leading to discontinuation were 2 cases each of nausea/vomiting and elevated amylase. Other adverse events leading to discontinuation were hallucinations, pneumonia, headache, injection site reaction, and abnormal gait. Dizziness and injection site pain were observed more frequently at a 100 mg/min infusion rate than at rates up to 33 mg/min. At a 200 mg/min rate, dizziness and taste perversion occurred more frequently than at a 100 mg/min rate. The maximum rate of infusion studied was 200 mg/min.

Adverse events reported by at least 0.5% of all subjects/patients in clinical trials of DEPACON are summarized in Table 1

Table 1
Adverse Events Reported During Studies of DEPACON

Body System/Event	N = 463
Body as a Whole	
Chest Pain	1.7%
Headache	4.3%
Injection Site Inflammation	0.6%
Injection Site Pain	2.6%
Injection Site Reaction	2.4%
Pain (unspecified)	1.3%
Cardiovascular	
Vasodilation	0.9%
Dermatologic	
Sweating	0.9%
Digestive System	
Abdominal Pain	1.1%
Diarrhea	0.9%
Nausea	3.2%
Vomiting	1.3%
Nervous System	
Dizziness	5.2%
Euphoria	0.9%
Hypesthesia	0.6%
Nervousness	0.9%
Paresthesia	0.9%
Somnolence	1.7%
Tremor	0.6%
Respiratory	
Pharyngitis	0.6%
Special Senses	
Taste Perversion	1.9%

Ammonia levels have not been systematically studied after IV valproate, so that an estimate of the incidence of hyperammonemia after IV Depacon cannot be provided. Hyperammonemia with encephalopathy has been reported in 2 patients after ~~/~~ infusions of Depacon.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE (divalproex sodium) was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 2 lists treatment-emergent adverse events which were reported by ≥ 5% of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 2
Adverse Events Reported by ≥ 5% of Patients Treated with DEPAKOTE During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Depakote (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4

Other		
Alopecia	6	1
Weight Loss	6	0

Table 3 lists treatment-emergent adverse events which were reported by ≥ 5% of patients in the high dose DEPAKOTE group, and for which the incidence was greater than in the low dose group, in a controlled trial of DEPAKOTE monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs

Table 3
Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of DEPAKOTE Monotherapy for Complex Partial Seizures[1]

Body System/Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

[1]Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with DEPAKOTE in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin.
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients using oral therapy.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonsim. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General** and **Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see **WARNINGS**).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic: Acute pancreatitis including fatalities (see **WARNINGS**).

Metabolic: Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other: Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

Mania

Although DEPACON has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE (DIVALPROEX SODIUM) tablets.

Body as a Whole: Chills, neck pain, neck rigidity.

Cardiovascular System: Hypotension, postural hypotension, vasodilation.

Digestive System: Fecal incontinence, gastroenteritis, glossitis.

Musculoskeletal System: Arthrosis.

Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

Skin and Appendages: Furunculosis, maculopapular rash, seborrhea.

Special Senses: Conjunctivitis, dry eyes, eye pain.

Urogenital: Dysuria.

Migraine
Although DEPACON has not been evaluated for safety and efficacy in the prophylactic treatment of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE (DIVALPROEX SODIUM) tablets.

Body as a Whole: Face edema
Digestive System: Dry mouth, stomatitis.
Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate serum concentrations as high as 2120 μg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepilepsy effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

DEPACON IS FOR INTRAVENOUS USE ONLY.

Use of DEPACON for periods of more than 14 days has not been studied. Patients should be switched to oral valproate products as soon as it is clinically feasible.

DEPACON should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary.

Initial Exposure to Valproate:
The following dosage recommendations were obtained from studies utilizing oral divalproex sodium products.

Complex Partial Seizures: For adults and children 10 years of age or older.

Monotherapy (Initial Therapy): DEPACON has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should 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. 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). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 µg/mL in females and 135 µg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should 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. 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 - 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of DEPACON therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy: DEPACON may be added to the patient's regimen 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. 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). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE (divalproex sodium), no adjustment of carbamazepine or phenytoin dosage was needed (see **CLINICAL STUDIES**). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see **Drug Interactions**), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see **PRECAUTIONS - Drug Interactions**).

Simple and Complex Absence Seizures: The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 µg/mL. Some patients may be controlled with lower or higher serum concentrations (see **CLINICAL PHARMACOLOGY**).

As the DEPACON dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see **PRECAUTIONS**).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Replacement Therapy:
When switching from oral valproate products, the total daily dose of DEPACON should be equivalent to the total daily dose of the oral valproate product (see **CLINICAL PHARMACOLOGY**), and should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary. Patients receiving doses near the maximum recommended daily dose of 60 mg/kg/day, particularly those not receiving enzyme-inducing drugs, should be monitored more closely. If the total daily dose exceeds 250 mg, it should be given in a divided regimen. There is no experience with more rapid infusions in patients receiving Depacon as replacement therapy. However, the equivalence shown between DEPACON and oral valproate products (DEPAKOTE) at steady state was only evaluated in an every 6 hour regimen. Whether, when DEPACON is given less frequently (i.e., twice or three times a day), trough levels fall below those that result from an oral dosage form given via the same regimen, is unknown. For this reason, when DEPACON is given twice or three times a day, close monitoring of trough plasma levels may be needed.

General Dosing Advice
Dosing in Elderly Patients - Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see **WARNINGS**).

Dose-Related Adverse Events - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of $\geq$ 110 µg/mL (females) or $\geq$ 135 µg/mL (males) (see **PRECAUTIONS**). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Administration
Rapid infusion of DEPACON has been associated with an increase in adverse events. There is limited experience with infusion times of less than 60 minutes or rates of infusion > 20 mg/min in patients with epilepsy (see **ADVERSE REACTIONS**).

DEPACON should be administered intravenously as a 60 minute infusion, as noted above. It should be diluted with at least 50 mL of a compatible diluent. Any unused portion of the vial contents should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Compatibility and Stability
DEPACON was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinyl chloride (PVC) bags at controlled room temperature 15-30°C (59-86°F).

- dextrose (5%) injection, USP
- sodium chloride (0.9%) injection, USP
- lactated ringer's injection, USP

HOW SUPPLIED

DEPACON (valproate sodium injection), equivalent to 100 mg of valproic acid per mL, is a clear, colorless solution in 5 mL single-dose vials, available in trays of 10 vials (**NDC** 0074-1564-10).

Recommended storage: Store vials at controlled room temperature 15-30°C (59-86°F). No preservatives have been added. Unused portion of container should be discarded.

Revised: June 2000

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

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/s/

Russell Katz
5/3/01 09:52:09 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

LABELING

(No. 1564)

DEPACON®
VALPROATE SODIUM INJECTION

R_x only

BOX WARNING:

HEPATOTOXICITY:

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPACON IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

TERATOGENICITY:

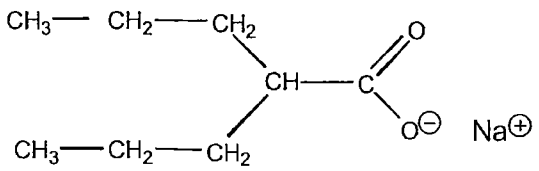
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF VALPROATE PRODUCTS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS.

PANCREATITIS:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See **WARNINGS** and **PRECAUTIONS**.)

DESCRIPTION

Valproate sodium is the sodium salt of valproic acid designated as sodium 2-propylpentanoate. Valproate sodium has the following structure:



Valproate sodium has a molecular weight of 166.2. It occurs as an essentially white and odorless, crystalline, deliquescent powder.

DEPACON solution is available in 5 mL single-dose vials for intravenous injection. Each mL contains valproate sodium equivalent to 100 mg valproic acid, edetate disodium 0.40 mg, and water for injection to volume. The pH is adjusted to 7.6 with sodium hydroxide and/or hydrochloric acid. The solution is clear and colorless.

CLINICAL PHARMACOLOGY

DEPACON exists as the valproate ion in the blood. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics

Bioavailability

Equivalent doses of intravenous (IV) valproate and oral valproate products are expected to result in equivalent C_{max}, C_{min}, and total systemic exposure to the valproate ion when the IV valproate is administered as a 60 minute infusion. However, the rate of valproate ion absorption may vary with the formulation used. These differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

Administration of DEPAKOTE (divalproex sodium) tablets and IV valproate (given as a one hour infusion), 250 mg every 6 hours for 4 days to 18 healthy male volunteers resulted in equivalent AUC, C_{max}, C_{min} at steady state, as well as after the first dose. The T_{max} after IV DEPACON occurs at the end of the one hour infusion, while the T_{max} after oral dosing with DEPAKOTE occurs at approximately 4 hours. Because the kinetics of unbound valproate are linear, bioequivalence between DEPACON and DEPAKOTE up to the maximum recommended dose of 60 mg/kg/day can be assumed. The AUC and C_{max} resulting from administration of IV valproate 500 mg as a single one hour infusion and a single 500 mg dose of DEPAKENE syrup to 17 healthy male volunteers were also equivalent.

Patients maintained on valproic acid doses of 750 mg to 4250 mg daily (given in divided doses every 6 hours) as oral DEPAKOTE (divalproex sodium) alone (n=24) or with another stabilized antiepileptic drug [carbamazepine (n=15), phenytoin (n=11), or phenobarbital (n=1)], showed comparable plasma levels for valproic acid when switching from oral DEPAKOTE to IV valproate (1-hour infusion).

Eleven healthy volunteers were given single infusions of 1000mg IV valproate over 5, 10, 30, and 60 minutes in a 4-period crossover study. Total valproate concentrations were measured; unbound concentrations were not measured. After the 5 minute infusions (mean rate of 2.8 mg/kg/min), mean Cmax was 145 ± 32 μg/mL, while after the 60 minute infusions, mean Cmax was 115 ± 8 μg/mL. Ninety to 120 minutes after infusion initiation, total valproate concentrations were similar for all 4 rates of infusion. Because protein binding is nonlinear at higher total valproate concentrations, the corresponding increase in unbound Cmax at faster infusion rates will be greater.

Distribution

Protein Binding:

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See **PRECAUTIONS, Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution:

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean terminal half-life for valproate monotherapy after an intravenous infusion of 1000 mg was 16 ± 3.0 hours.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations

Effect of Age:

Neonates - Children within the first two months of life have a markedly decreased ability to

eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children - Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly - The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See **DOSAGE AND ADMINISTRATION**).

Effect of Gender:
There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).

Effect of Race:
The effects of race on the kinetics of valproate have not been studied.

Effect of Disease:
Liver Disease - (See **BOXED WARNING, CONTRAINDICATIONS,** and **WARNINGS**). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease - A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent,

the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy:
The therapeutic range in epilepsy is commonly considered to be 50 to 100 μg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Equivalent doses of DEPACON and DEPAKOTE (divalproex sodium) yield equivalent plasma levels of the valproate ion (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Clinical Studies
The studies described in the following section were conducted with oral divalproex sodium products.

Epilepsy
The efficacy of DEPAKOTE (divalproex sodium) in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

In one, multiclinic, placebo controlled study employing an add-on design (adjunctive therapy), 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

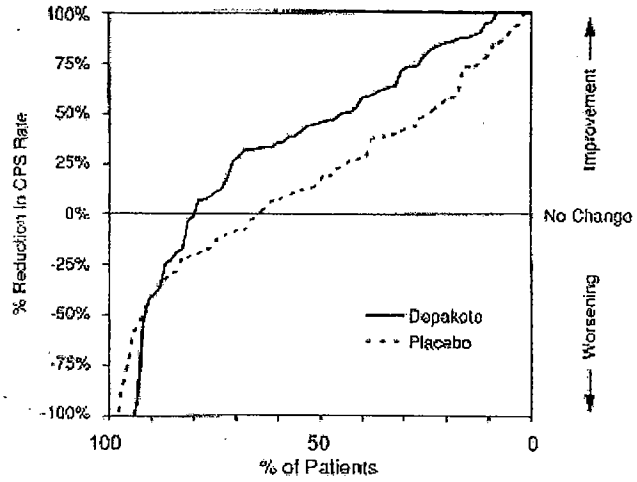
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at $p \leq 0.05$ level.

Figure 1 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a $\geq$ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 1



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 μg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

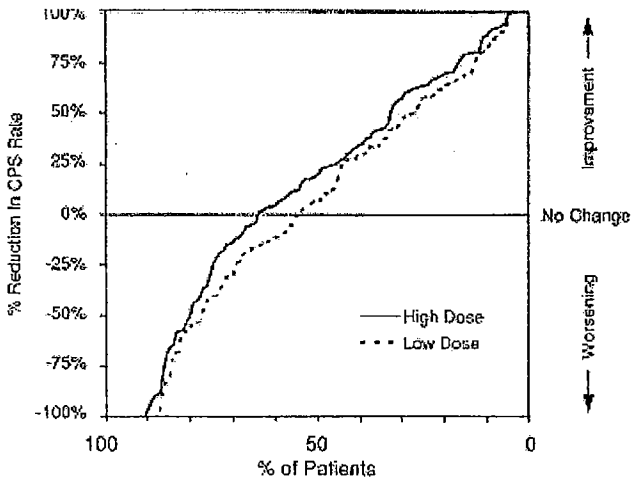
Monotherapy Study
Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose DEPAKOTE	131	13.2	10.7*
Low dose DEPAKOTE	134	14.2	13.8

*Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose DEPAKOTE.

Figure 2



INDICATIONS AND USAGE

DEPACON is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

DEPACON is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPACON is also indicated for use as sole and adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE **WARNINGS** FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION

CONTRAINDICATIONS

VALPROATE SODIUM INJECTION SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Valproate sodium injection is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months of valproate therapy. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering valproate products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPACON is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Use of DEPACON has not been studied in children below the age of 2 years. Above this age group, experience with valproate products in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily

be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see **BOXED WARNING**).

Somnolence in the Elderly
In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**).

Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see **PRECAUTIONS**]) may be dose-related. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Post-traumatic Seizures

A study was conducted to evaluate the effect of IV valproate in the prevention of post-traumatic seizures in patients with acute head injuries. Patients were randomly assigned to receive either IV valproate given for one week (followed by oral valproate products for either one or six months per random treatment assignment) or IV phenytoin given for one week (followed by placebo). In this study, the incidence of death was found to be higher in the two groups assigned to valproate treatment compared to the rate in those assigned to the IV phenytoin treatment group (13% vs 8.5%, respectively). Many of these patients were critically ill with multiple and/or severe injuries, and evaluation of the causes of death did not suggest any specific drug-related causation. Further, in the absence of a concurrent placebo control during the initial week of intravenous therapy, it is impossible to determine if the mortality rate in the patients treated with valproate was greater or less than that expected in a similar group not treated with valproate, or whether the rate seen in the IV phenytoin treated patients was lower than would be expected. Nonetheless, until further information is available, it seems prudent not to use DEPACON in patients with acute head trauma for the prophylaxis of post-traumatic seizures.

Usage In Pregnancy

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPSY DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPSY DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (E.G., CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPSY DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 μg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200

mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 µg/mL or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/mL (2.8 times the upper limit of the human therapeutic range).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepilepsy drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction
See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**

Pancreatitis
See **BOXED WARNING** and **WARNINGS.**

General
Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPACON be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE (divalproex sodium) as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of

≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPACON therapy should be modified or discontinued.

Since DEPACON may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See **PRECAUTIONS - Drug Interactions**).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Information for Patients

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Since DEPACON may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor

could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed:
Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Felbamate - A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 μg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 μg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:
Antacids - A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine - A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyl transferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed:
Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a

21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10,11-Epoxide - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam - The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam - Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine - In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate.

Phenobarbital - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin - Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was

increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin - In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproate therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Acetaminophen - Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine - In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium - Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam - Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids - Administration of a single-dose of ethinyloestradiol (50 μg)/levonorgestrel (250 μg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy

Pregnancy Category D: See **WARNINGS**.

Nursing Mothers

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when valproate is administered to a nursing woman.

Pediatric Use

Experience with oral valproate has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see **BOXED WARNING**). The safety of DEPACON has not been studied in individuals below the age of 2 years. If a decision is made to use DEPACON in this age group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

No unique safety concerns were identified in the 35 patients age 2 to 17 years who received DEPACON in clinical trials.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see **WARNINGS–Somnolence in the Elderly**). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**)

No unique safety concerns were identified in the 21 patients > 65 years of age receiving DEPACON in clinical trials.

ADVERSE REACTIONS

The adverse events that can result from DEPACON use include all of those associated with oral forms of valproate. The following describes experience specifically with DEPACON. DEPACON has been generally well tolerated in clinical trials involving 111 healthy adult male volunteers and 352 patients with epilepsy, given at doses of 125 to 6000 mg (total daily dose). A total of 2% of patients discontinued treatment with DEPACON due to adverse events. The most common adverse events leading to discontinuation were 2 cases each of nausea/vomiting and elevated amylase. Other adverse events leading to discontinuation were hallucinations, pneumonia, headache, injection site reaction, and abnormal gait. Dizziness and injection site pain were observed more frequently at a 100 mg/min infusion rate than at rates up to 33 mg/min. At a 200 mg/min rate, dizziness and taste perversion occurred more frequently than at a 100 mg/min rate. The maximum rate of infusion studied was 200 mg/min.

Adverse events reported by at least 0.5% of all subjects/patients in clinical trials of DEPACON are summarized in Table 1

Table 1
Adverse Events Reported During Studies of DEPACON

Body System/Event	N = 463
Body as a Whole	
Chest Pain	1.7%
Headache	4.3%
Injection Site Inflammation	0.6%
Injection Site Pain	2.6%
Injection Site Reaction	2.4%
Pain (unspecified)	1.3%
Cardiovascular	
Vasodilation	0.9%
Dermatologic	
Sweating	0.9%
Digestive System	
Abdominal Pain	1.1%
Diarrhea	0.9%
Nausea	3.2%
Vomiting	1.3%
Nervous System	
Dizziness	5.2%
Euphoria	0.9%
Hypesthesia	0.6%
Nervousness	0.9%
Paresthesia	0.9%
Somnolence	1.7%
Tremor	0.6%
Respiratory	
Pharyngitis	0.6%
Special Senses	
Taste Perversion	1.9%

In a separate clinical safety trial, 112 patients with epilepsy were given infusions of Depacon (up to 15mg/kg) over 5 to 10 minutes (1.5-3.0 mg/kg/min). The common adverse events (>2%) were somnolence (10.7%), dizziness (7.1%), paresthesia (7.1%), asthenia (7.1%), nausea (6.3%) and headache (2.7%). While the incidence of these adverse events was generally higher than in Table 1 (experience encompassing the standard, much slower infusion rates), e.g. somnolence (1.7%), dizziness (5.2%), paresthesia (0.9%), asthenia (0%), nausea (3.2%), and headache (4.3%), a direct comparison between the incidence of adverse events in the 2 cohorts cannot be made because of differences in patient populations and study designs.

Ammonia levels have not been systematically studied after IV valproate, so that an estimate of the incidence of hyperammonemia after IV Depacon cannot be provided. Hyperammonemia with encephalopathy has been reported in 2 patients after infusions of Depacon.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE (divalproex sodium) was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 2 lists treatment-emergent adverse events which were reported by ≥ 5% of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 2
Adverse Events Reported by ≥ 5% of Patients Treated with DEPAKOTE During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Depakote (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 3 lists treatment-emergent adverse events which were reported by ≥ 5% of patients in the high dose DEPAKOTE group, and for which the incidence was greater than in the low dose group, in a controlled trial of DEPAKOTE monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs

Table 3
Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of DEPAKOTE Monotherapy for Complex Partial Seizures[1]

Body System/Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

[1]Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with DEPAKOTE in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin.
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients using oral therapy.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonsim. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General** and **Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see **WARNINGS**).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic: Acute pancreatitis including fatalities (see **WARNINGS**).

Metabolic: Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other: Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

Mania

Although DEPACON has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE (DIVALPROEX SODIUM) tablets.

Body as a Whole: Chills, neck pain, neck rigidity.

Cardiovascular System: Hypotension, postural hypotension, vasodilation.

Digestive System: Fecal incontinence, gastroenteritis, glossitis.

Musculoskeletal System: Arthrosis.

Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

Skin and Appendages: Furunculosis, maculopapular rash, seborrhea.

Special Senses: Conjunctivitis, dry eyes, eye pain.

Urogenital: Dysuria.

Migraine
Although DEPACON has not been evaluated for safety and efficacy in the prophylactic treatment of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE (DIVALPROEX SODIUM) tablets.

Body as a Whole: Face edema
Digestive System: Dry mouth, stomatitis.
Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate serum concentrations as high as 2120 µg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepilepsy effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

DEPACON IS FOR INTRAVENOUS USE ONLY.

Use of DEPACON for periods of more than 14 days has not been studied. Patients should be switched to oral valproate products as soon as it is clinically feasible.

DEPACON should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary.

In one clinical safety study, approximately 90 patients with epilepsy and with no measurable plasma levels of valproate were given single infusions of Depacon (up to 15mg/kg and mean dose of 1184mg) over 5-10 minutes (1.5-3.0mg/kg/min). Patients generally tolerated the more rapid infusions well (see **ADVERSE REACTIONS**). This study was not designed to assess the effectiveness of these regimens. For pharmacokinetics with rapid infusions, see **CLINICAL PHARMACOLOGY, Pharmacokinetics – Bioavailability.**

Initial Exposure to Valproate:
The following dosage recommendations were obtained from studies utilizing oral divalproex sodium products.

Complex Partial Seizures: For adults and children 10 years of age or older.

Monotherapy (Initial Therapy): DEPACON has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should 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. 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). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/mL in females and 135 μg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should 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. 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 - 100 μg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of DEPACON therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy: DEPACON may be added to the patient's regimen 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. 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). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE (divalproex sodium), no adjustment of carbamazepine or phenytoin dosage was needed (see **CLINICAL STUDIES**). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see **Drug Interactions**), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see **PRECAUTIONS - Drug Interactions**).

Simple and Complex Absence Seizures: The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 μg/mL. Some patients may be controlled with lower or higher serum concentrations (see **CLINICAL PHARMACOLOGY**).

As the DEPACON dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see **PRECAUTIONS**).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Replacement Therapy:
When switching from oral valproate products, the total daily dose of DEPACON should be equivalent to the total daily dose of the oral valproate product (see **CLINICAL PHARMACOLOGY**), and should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary. Patients receiving doses near the maximum recommended daily dose of 60 mg/kg/day, particularly those not receiving enzyme-inducing drugs, should be monitored more closely. If the total daily dose exceeds 250 mg, it should be given in a divided regimen. There is no experience with more rapid infusions in patients receiving Depacon as replacement therapy. However, the equivalence shown between DEPACON and oral valproate products (DEPAKOTE) at steady state was only evaluated in an every 6 hour regimen. Whether, when DEPACON is given less frequently (i.e., twice or three times a day), trough levels fall below those that result from an oral dosage form given via the same regimen, is unknown. For this reason, when DEPACON is given twice or three times a day, close monitoring of trough plasma levels may be needed.

General Dosing Advice
Dosing in Elderly Patients - Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see **WARNINGS**).

Dose-Related Adverse Events - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of $\geq$ 110 μg/mL (females) or $\geq$ 135 μg/mL (males) (see **PRECAUTIONS**). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Administration
Rapid infusion of DEPACON has been associated with an increase in adverse events. There is limited experience with infusion times of less than 60 minutes or rates of infusion > 20 mg/min in patients with epilepsy (see **ADVERSE REACTIONS**).

DEPACON should be administered intravenously as a 60 minute infusion, as noted above. It should be diluted with at least 50 mL of a compatible diluent. Any unused portion of the vial contents should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Compatibility and Stability

DEPACON was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinyl chloride (PVC) bags at controlled room temperature 15-30°C (59-86°F).

- dextrose (5%) injection, USP
- sodium chloride (0.9%) injection, USP
- lactated ringer's injection, USP

HOW SUPPLIED

DEPACON (valproate sodium injection), equivalent to 100 mg of valproic acid per mL, is a clear, colorless solution in 5 mL single-dose vials, available in trays of 10 vials (**NDC** 0074-1564-10).

Recommended storage: Store vials at controlled room temperature 15-30°C (59-86°F). No preservatives have been added. Unused portion of container should be discarded.

Revised: June 2000

ABBOTT

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

MEDICAL REVIEW

Review and Evaluation of Clinical Data

IND (Serial Number)	**20-593/S-006**
Sponsor:	**Abbott Laboratories**
Drug:	**Depacon (Valproate Sodium Injection 500mg/5cc intravenously)**

Material Submitted:	**Supplemental NDA based on Phase IIIb safety and tolerability study M98-938: "Safety and Tolerance of Intravenous Depacon at an Infusion Rate up to 3.0 mg/kg/minute in Subjects with Epilepsy" (Report R&D/99/674: Clinical/Safety information) Supplement Amendment (September 15, 2000): "Response to FDA Request for Information"**
Correspondence Date:	**June 30, 2000**
Date Received / Agency:	**July 3, 2000**
Date Review Completed	**April 30, 2001**
Reviewer:	**Philip H. Sheridan, M.D.**

I. INTRODUCTION

The original NDA for intravenous sodium valproate (Depacon) was approved in 1996 (NDA 20-593).

The indication in current labeling for Depacon is as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

(1) Monotherapy and adjunctive therapy of patients with complex partial seizures in isolation or in association with other seizure types

(2) Sole and adjunctive therapy of patients with simple and complex absence seizures

(3) Adjunctive therapy of patients with multiple seizures types that include absence seizures.

Current labeling recommends administration of Depacon as a one-hour infusion at a rate not exceeding 20 mg/min. [For a 70-kg adult, this rate would be approximately 0.3 mg/kg/min.] Current labeling recommends that the intravenous doses be given at the same frequency (every 6 hours) as the oral valproate product (which it is temporarily replacing) although plasma monitoring and dosing adjustments may be necessary. It is not recommended for use over more than fourteen days.

The Sponsor proposed a rapid infusion study of valproate sodium injection in their November 25, 1998 submission to IND 32,231 (Serial No. 075). A draft protocol was submitted on February 4, 1999 (Serial No. 77). In the February 26, 1999 teleconference with DNDP, the Sponsor indicated that the intended purpose of study M98-938 was to provide data to support the rapid infusion of Depacon in clinical situations where the rapid attainment of steady state valproate levels in patients with low or absent serum levels is desired. The Sponsor study results were not intended to modify or expand on the currently approved indications.

The present Supplemental New Drug Application provides pharmacokinetic and safety information from a Phase IIIB safety and tolerability study at infusion rates up to 3.0 mg/kg/min in epileptic patients.

Although oral valproate products have indications in their current labeling for migraine prophylaxis and for manic episodes associated with bipolar disorder, Depacon does not. The recent published medical literature includes published reports of the use of Depacon in treating these conditions. Furthermore, there are published reports for the use of valproate for status epilepticus (Sinha S and Naritoku DK , *Neurology*, 2000), migraine status (Norton J, *Headache,* Oct 2000), and the initial treatment of acute mania (Swann AC, *Am J Psych* 1999).
[ ] Depakote [ ] have these indications in their current labeling,

[redacted]

II. REVIEW AND REVIEWER'S ASSESSMENT

1. Protocol M 98-938

1.1 Objective

The primary objective is to evaluate the **safety** of rapidly infusing Depacon at a rate of 1.5 mg/kg/min or 3.0 mg/kg/min for a total dose of up to 15 mg/kg in patients with epilepsy.

The secondary objective is to evaluate the relationship between valproate administration and adverse events observed with this dosing strategy.

1.2 Design

This was a multicenter open-label prospective randomized parallel study with epileptic patients.

The study had **two phases**: an infusion phase and an optional maintenance phase.

In **the infusion phase**, each patient received up to four intravenous infusions of Depacon over a 24-hour period with at least 2 hours separating each infusion. The first infusion was 15 mg/kg given over about 10 minutes (1.5 mg/kg/min) or about 5 minutes (3.0 mg/kg/min). Any additional infusion dose was calculated for the individual patient to target a plasma valproate concentration of 50-100 ug/ml (with a maximum dose of 15 mg/kg for each infusion). Most patients were expected to require only the initial Depakote infusion to reach the target drug level; in fact, only two patients required a second infusion as discussed below. After the target plasma valproate concentration reached 50-100 ug/ml (or the investigator determined that the concentration was adequate), the option existed for the patient to either be switched to an oral valproate product outside the protocol or to continue on Depacon in **the maintenance phase** of the study for up to fourteen days.

Medical and seizure histories, abbreviated physical examination, laboratory tests (hematology, chemistry, and valproate level), and brief neurological and cardiology examinations determined a patient's eligibility. A baseline EKG was also performed.

If the patient met entrance criteria (below), the patient was randomized in a 2:1 ratio at each center to receive either the 3.0-mg/kg/min infusion (70 patients planned) or the 1.5 mg/kg/min infusion (35 patients planned) for a total dose of up to 15 mg/kg per infusion and up to 60 mg/kg over 24 hours.

During the infusion phase, patients were monitored for adverse events during and after the infusion(s). Serial blood pressure measurements (pre-infusion at 5 minutes as well as after infusion at end-of-infusion and at 5, 10, 20, and 30 minutes post-infusion) were recorded. Continuous EKG cardiac rhythm monitoring was performed during the infusion and for five minutes post-infusion. If any abnormal rhythm changes were noted, the monitoring continued until these changes resolved. A change in the EKG significant enough to lead to patient discontinuation from the study was considered an adverse event

A preinfusion blood valproate level (free and total) was used to determine study eligibility. All eligible patients received a dose of 15 mg/kg. Blood valproate levels (free and total) were drawn 5 minutes post infusion, 30 minutes post infusion (optional), and every hour for 6 hours after the infusion.

Only two patients (both in the 3.0 mg./kg./min group) required a second infusion during the infusion phase of the study. Each subject's need for a subsequent infusion was determined from the 1-hour post infusion measurement. If the patient's level was below the usual therapeutic range (50-100 mcg/ml), a subsequent infusion of up to 15 mg/kg would be given as calculated from a formula based on body weight and estimated volume of distribution.

If used, oral maintenance Depakote was begun outside the study protocol by the patient's treating physician at a time beyond 6 hours post infusion (to allow completion of the study's pharmacokinetic component) and at a dose determined by the patient's treating physician.

A follow-up visit occurred one week after the final Depacon infusion.

1.3 Sample Size

Twelve of the thirteen sites enrolled patients.

112 randomized subjects were treated with Depacon.

The sample size was calculated to allow the detection of a difference of 10-mm Hg between the treatment group averages of the 5-min post-first-infusion systolic blood pressures with at least 80 % power.

1.4 Key Inclusion Criteria

Epilepsy with complex partial or absence seizure types

Clinical indication for rapid infusion of Depacon

Valproate level 0 - <50 ug/ml

At least 2 years of age

Male or non-lactating female (using effective birth control if of child-bearing potential)

1.5 Key Exclusion Criteria

Status epilepticus at study onset or within 24 hours prior to study onset (amended to within 30 days prior to study onset)

Serial seizures or flurries of seizures within 24 hours prior to study onset

History of significant cardiac, renal, neurologic, psychiatric, oncologic, endocrinologic, metabolic, or hepatic disease

Clinical or serologic history of hepatitis or thrombocytopenia

History of Lennox-Gastaut syndrome or Continuous Spike Wave in Sleep (CSWS)

History of cardiac rhythm disturbances, orthostatic hypotension, or syncope

History of drug or alcohol abuse

Experimental drug or felbamate within 30 days prior to study day 1

Recent cardioactive drugs

History of adverse reaction to study drug or similar drugs

1.6 Concomitant Medications

Induced vs. non-induced patients

Permitted: Most OTC and prescription medications. Lamotrigine doses to be adjusted by the investigator as needed due to inhibition of clearance by valproate.

Prohibited: beta-blockers, cardiac inotropes/pressors, alpha-adrenergic medications, anti-arrhythmic medications, felbamate, and experimental medications

1.7 Dosage

All but two patients received a single intravenous infusion of Depacon (15 mg/kg) given over about 10 minutes (1.5 mg/kg/min) or about 5 minutes (3.0 mg/kg/min). Two patients (both having received 3.0 mg/kg/min infusions) were found to be below the target level of 50-100 ug/ml after the first infusion. These two patients

each received a second infusion calculated for the individual patient to target a plasma valproate concentration of 50-100 ug/ml (with a maximum dose of 15 mg/kg.) No patients required a third infusion.

1.8 Outcome Measure

(i) Compare VPA pharmacokinetics in subjects receiving Depacon at a rate of 1.5 vs. 3.0 mg/kg/min and in induced vs. non-induced subjects
(ii) Determine predictors of C-max and clearance as a function of demographics and dosing rate.
(iii) Identify significant factors affecting the binding of VPA to albumin.
(iv) Assess the accuracy of dosing and re-dosing strategy employed using subject weight and an assumed population volume of distribution
(v) Evaluate the association for adverse events with VPA plasma concentrations.

1.9 Analysis Plan

Efficacy Analysis
This is not an efficacy trial.

Safety Analysis
Adverse events (including EKG cardiac monitoring), clinical laboratory data, and blood pressure recordings were used to evaluate safety.

Statistical Methods
All tests were two tailed at 0.05 level of significance.

All patients treated with Depacon were evaluated.

Patients were analyzed according to the treatment group that they came closest to receiving. Patients whose first infusion was at a rate <2.25 mg/kg/min were grouped under the 1.5 mg/kg/min group. Patients whose **first** infusion was at a rate >2.25 mg/kg/min were grouped under the 3.0 mg/kg/min group. This resulted in 9 patients having their randomization assignments changed as discussed below under Results.

The number and percentage of patients having treatment-emergent adverse effects were tabulated by COSTART term and body system as well as by severity and perceived relationship to Depacon. Adverse events emerging during or within 6 hours following the first infusion were also summarized. Treatment group differences were assessed for each body system and COSTART term with Fisher's exact test, ignoring severity and relationship to Depacon.

The **primary endpoints for treatment group differences in systolic and diastolic blood pressure** were the change from baseline to the 5-minute post-infusion measure and to the minimum value following the first infusion. The study also evaluated changes from baseline in blood pressures to the end of the infusion, to the 10-, 20-, and 30-minute post-infusion measures, and to the maximum value following the first infusion.

All adverse events (reported by patient in response to query, observed by study personnel, or spontaneously reported by patient) were recorded on the case report form (CRF). An abnormal laboratory value was considered an adverse event only when it required premature study discontinuation, required treatment, or met regulatory criteria for a serious adverse event.

1.10 Safety Monitoring

Discussed under 1.9 Safety analysis.

An independent safety committee of neurology experts and a statistician was appointed to review all case of status epilepticus occurring during the course of the study, but none were reported.

All subjects but two received only a single infusion of Depacon. Therefore analyses of changes from baseline in diastolic and systolic blood pressure were restricted to measurements taken following the first infusion. The last measurement taken prior to the first infusion served as the baseline in all of these analyses.

2. Results

2.1 Enrollment, Randomization, and Actual Infusion Rates:

As shown in Table 6.1a (below) from the Sponsor's final report, a total of 112 patients were enrolled from 12 of the 13 participating sites. Thirty-seven patients were randomized to the slower (1.5 mg/min/kg over 10 minutes) infusion and seventy-five patients were randomized to the faster (3.0 mg/min/kg over 5 minutes) infusion. Three of the patients randomized to the slower infusion actually were infused at a rate closer to the faster infusion and thus were analyzed (categorized) with the faster infusion group. In the same fashion, six of the patients randomized to the faster infusion were found to have been infused at a rate closer to the slow infusion and were thus analyzed with the slower infusion group. The nine specific patients involved are identified in Table 10.2a reproduced below (under 2.2 Protocol Deviations).

Because of these reassignments, the number of patients analyzed with the slower infusion group changed from 37 to 40 and the number of patients analyzed with the higher rate changed to from 75 to 72.

In the appendix of the final report, the Sponsor also analyzed the data according to the original randomization irrespective of the actual infusion rate (i.e. not changing the assignment of the nine patients) and obtained similar results with regard to the comparative safety and tolerability of the two infusion rates.

Table 6.1a Distribution of Subjects by Investigator and Randomized Treatment Group

		Depacon® Randomized Treatment Group[a]	
Investigator	Enrolled	1.5 mg/kg/minute	3.0 mg/kg/minute
Cantrell	20	7 (1)	13 (1)
Cloyd	6	2	4
Gates	11	4	7
Kanner	6	2	4
Kuzniecky	7	2	5 (3)
Labiner	2	1	1
Montouris	6	1	5 (1)
Morris	7	2 (1)	5
Naritoku	15	5	10
Pellock	6	2 (1)	4 (1)
Ramsay	20	6	14
Vazquez	6	3	3
Wheless	0	0	0
Total	112	37 (3)	75 (6)

[a] The actual infusion rates (in mg/kg/minute) for the first infusion ranged from 1.00 to 3.00 for subjects randomized to the 1.5 mg/kg/minute treatment group and from 1.50 to 3.72 for subjects randomized to the 3.0 mg/kg/minute treatment group. Number in parentheses is the number of subjects whose first infusion rate was closer to the opposite treatment. For example, at investigator Pellock's site, 1 of the 2 subjects randomized to the 1.5 mg/kg/minute treatment group received >2.25 mg/kg/minute and 1 of the 4 subjects randomized to the 3.0 mg/kg/minute treatment group received <2.25 mg/kg/minute (for further discussion, please see Section 10.2).

The actual distribution of infusion rates is shown in Table 10.1a of the Sponsor's final report and is reproduced below.

Appears This Way
On Original

Table 10.1a Distribution of Infusion Rate Received in First Infusion			
Randomized Depacon® Treatment Group			
1.5 mg/kg/minute (N=37)		3.0 mg/kg/minute (N=75)	
Rate Received	Number of Subjects	Rate Received	Number of Subjects
1.0 - 1.1	2	>1.4 - 1.5	1
>1.3 - 1.4	1	>1.9 - 2.0	2
>1.4 - 1.5	26	>2.0 - 2.1	1
>1.5 - 1.6	1	>2.1 - 2.25	2
>1.6 - 1.7	2	>2.3 - 2.4	1
>1.8 - 1.9	1	>2.4 - 2.5	2
>1.9 - 2.0	1	>2.5 - 2.6	2
>2.4 - 2.5	1	>2.8 - 2.9	1
>2.9 - 3.0	2	>2.9 - 3.0	52
		>3.0 - 3.1	6
		>3.2 - 3.3	2
		>3.3 - 3.4	1
		>3.6 - 3.7	1
		>3.7 - 3.8	1

This table indicates that the majority of patients randomized to each infusion rate received their infusion at or very close to that rate. It is consistent with the Sponsor's protocol deviation summary table (10.2a shown below under 2.2 Protocol Deviations) which indicates that (after the rate group reassignment discussed above), 30/40 of the slow infusion group and 61/72 of the faster infusion group did not receive an infusion rate which was >0.1 mg/kg/min different from the targeted rate.

In the Sponsor's Table 12.1a (below), a slightly smaller number of patients is indicated as receiving their infusions within 0.1 mg/kg/min of the categorized (reassigned) infusion group: 28/40 of the slow infusion and 60/72 of the faster infusion group. This slight discrepancy does not change the overall observation that the study was able to achieve the targeted infusion rates with acceptable

Table 12.1a Infusion Phase Depacon® Administration		
	Depacon® Treatment Group	
	1.5 mg/kg/minute (N = 40)	3.0 mg/kg/minute (N = 72)
Mean (SD) Depacon® Dose Per Infusion		
First Infusion		
Mg	1184.4 (411.21)	1088.3 (363.10)
mg/kg	14.4 (1.54)	14.7 (1.08)
mg/kg/minute	1.6 (0.24)	3.0 (0.20)
Second Infusion		(N = 2)
Mg	n/a	464.5 (473.05)
mg/kg	n/a	12.5 (3.76)
mg/kg/minute	n/a	2.9 (0.52)
Distribution of Infusion Rate for the First Infusion n (%)		
More than 0.1 mg/kg/minute less[a]	3 (8%)	7 (10%)
Within ±0.1 mg/kg/minute[a]	28 (70%)	60 (83%)
More than 0.1 mg/kg/minute over[a]	9 (23%)	5 (7%)
n/a = not applicable		
[a] Versus categorized dose		

accuracy.

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The Sponsor reports that the two treatment groups did not differ statistically with regard to age, gender, race, years with epilepsy, history of seizure types, and number of antiepileptic drugs ever taken since diagnosis.

Table 11.2a from the Sponsor's final report shows the demographics of the 112 patients in the study, comparing the two treatment groups.

Demographics of Patients by Treatment Group

Demographic Characteristic	Depacon® Treatment Group n (%) 1.5 mg/kg/minute (N = 40)		Depacon® Treatment Group n (%) 3.0 mg/kg/minute (N = 72)		P-value
Sex					
Female	18	(45%)	33	(46%)	>0.999
Male	22	(55%)	39	(54%)	
Race					
Caucasian	28	(70%)	50	(69%)	0.348
African-American	10	(25%)	11	(15%)	
Asian/Pacific Islander	0	(0%)	2	(3%)	
Other	2	(5%)	9	(13%)	
Age (years)					0.474
Mean (SD)	37.7 (15.49)		35.5 (15.84)		
Min - Max	7.0 - 77.0		1.0 - 79.0		
Weight (kilograms)					0.116
Mean (SD)	81.6 (26.11)		73.8 (24.14)		
Min - Max	28.0 - 155.5		8.6 - 145.2		
Height (centimeters)	(N = 37)		(N = 63)		0.443
Mean (SD)	168.0 (13.90)		165.2 (19.52)		
Min - Max	125.0 - 198.1		72.5 - 193.0		

Cross-reference: Table 14.1__2.1

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On Original

A statistical comparison of the two groups with regard to the number of concomitant AED's, the number of patients already on valproate at enrollment (but still needing a full loading dose as required by the inclusion criteria), and the number of inducing concomitant drugs is not reported, but to my review the two groups are similar with respect to these factors.

In Section 11.2.2 (p. 64) of the Sponsor's final report, the patients were classified according to the reason for their entry into the study (that is, the patient's "clinical indication for rapid infusion of Depacon" which is a key inclusion criterion). The more common reason for enrolling in the study among subjects in both treatment groups was "epilepsy best treated with valproate with low or no plasma valproate levels" (68% and 79% in the 1.5 and 3.0 mg/kg/min treatment groups respectively). The remaining patients were enrolled in order to re-introduce valproate therapy (33% and 21% in the 1.5 and 3.0 mg/kg/min treatment groups (respectively). There were 40 patients in the 1.5 mg/kg/min group and 72 patients in the 3.0 mg/kg/min group. Therefore, there were a total of 84 patients **(75% of the 112 patients)** having low or no plasma valproate levels before the study infusion and 28 patients **(25% of the 112 patients)** who were given the study infusion to reintroduce valproate. All 112 patients received the full 15 mg/kg infusion of Depacon as required by the protocol.

The number of concomitant antiepileptic drugs used by patients in the two treatment groups are compared in Table 14.1_6 of the final study report.

Modified Table 14.1_6 from the Clinical Study Report (Vol. 4 Section 8.14)

Co-administered anti-epileptic medications used by at least 5% of the subjects in either treatment group

	Number (%) of subjects		
Anti-epileptic Drug	**1.5 mg/kg/min (n=40)**	**3.0 mg/kg/min (n=72)**	**Total (n=112)**
Carbamazepine*	**11 (27.5%)**	**14 (19.4%)**	**25 (22.3%)**
Lamotrigine	**7 (17.5%)**	**15 (20.8%)**	**22 (19.6%)**
Phenytoin*	**10 (25.0%)**	**12 (16.7%)**	**22 (19.6%)**
Tiagabine	**2 (5.0%)**	**1 (1.4%)**	**3 (2.7%)**
Phenobarbital*	**3 (7.5%)**	**5 (6.9%)**	**8 (7.1%)**
Primidone	**2 (5.0%)**	**0**	**2 (1.8%)**
Lorazepam	**3 (7.5%)**	**6 (8.3%)**	**9 (8.0%)**
Gabapentin	**5 (12.5%)**	**11 (15.3%)**	**16 (14.3%)**
Topiramate	**4 (10.0%)**	**6 (8.3%)**	**10 (8.9%)**

Inducer of valproate metabolism (lower valproate Cp's have been reported during concomitant therapy)

2.2 Protocol Deviations

Significant protocol deviations are summarized in Table 10.2a from the Sponsor's final report, reproduced below.

Table 10.2a Significant Protocol Deviations

Procedure	Description of Deviation	Subject Numbers Depacon® Treatment Group	
		1.5 mg/kg/minute	3.0 mg/kg/minute
Admission Criteria	History of syncope	205	202, 604, 908, 1201
	History of juvenile myoclonic epilepsy and partial simple seizures		102
	History of atrial fibrillation		201
	History of thrombocytopenia		716
	Treated with disallowed medication(s)	716, 914, 1104, 1107	202, 912
	Active alcohol abuser		103
	Positive for hepatitis B		406
	Pre-infusion plasma valproate concentration ≥50 µg/mL	603	303, 602
	Age at entry <2 years (13 months)		606
	Positive drug screen		709
Randomization	Failure of investigative site to assign subject numbers in ascending numerical order	603	602, 604
Infusion Phase			
Study Drug Administration	Volume of diluent was <50 mL and Depacon® to total volume ratio was <5.0 (prior to Amendment 1)	301, 703, 706, 714	302, 304, 305, 701, 702, 705, 709, 710, 711, 712, 713, 715, 716, 717, 719, 720
	Volume of diluent was <50 mL and Depacon® to total volume ratio was ≥5.0 (prior to Amendment 1)		401
	Volume of diluent was <50 mL, but Depacon® to total volume ratio was <5.0 (after Amendment 1)	306, 1103, 1107	1102, 1301
	Oral Depakote® given <6 hours post-infusion	404, 605	405, 1205
	Received an infusion rate closer to the opposite randomized rate	404, 603, 909, 1103, 1104, 1107	601, 907, 1204
	Received an infusion >0.1 mg/kg/minute different than the randomized rate that was not closer to the opposite randomized rate	605, 707, 901, 910, 1004, 1101, 1206	401, 405, 602, 715, 902, 903, 908, 913, 1001, 1003, 1005
	Received study drug from hospital or open stock		304, 601

I have reviewed the individual patient reports and have concluded that this table is complete.

Several of these deviations are interesting. A 13 month old (patient 606) was enrolled (inclusion criteria require age of two years or greater) and received the faster (3.0 mg/kg/min) infusion rate without adverse effects.

A 29 year old patient (patient 202) with a previous history of syncope and tachycardia who was also taking inderal for migraine prophylaxis was randomized to the 3.0 mg/kg/min group and attained a 5 minute post infusion level of valproate of 123. He did not have a significant change in either systolic or diastolic blood pressure compared to his baseline. He had only mild

lightheadedness 5 minutes into the infusion and nonspecific ST changes on his EKG. Similarly, a 54 year old patient (914) on verapamil for migraine prophylaxis was randomized to a 1.5 mg/kg/min infusion and had no significant change in either systolic or diastolic blood pressure compared to her baseline; she reported only nausea as an adverse effect.

Four patients with a history of syncope were randomized to the faster infusion rate compared to one patient with a syncopal history randomized to the slower infusion rate; this might have biased the study toward suggesting that the faster infusion was more likely to cause syncope but this was not found with regard to these specific patients (none of whom had syncope) or for the study overall.

None of the protocol deviations appear to have a potential for biasing the study's results.

2.3 Treatment - Emergent Adverse Effects

Table 12.2b from the final study report shows the most frequently reported adverse events (i.e. AE's occurring in at least 5% in either treatment group.)

The percent of patients experiencing these adverse events is approximately the same in each treatment group. The adverse events and their incidence are also similar to what is reported in the current Depacon labeling for Depacon and Depakote. Table 2 in the current Depacon labeling indicates that patients on Depakote during a placebo control study reported a higher incidence of somnolence, dizziness, and gastrointestinal adverse effects compared to the Depacon studies in current labeling or the study under review (M98-938). Depakote patients did not report the paresthesias reported in the Depacon studies. Patients in the two groups of M98-938 had a five to six fold higher incidence of somnolence (15%, 10%) and paresthesias ((5%, 8%) compared to patients in the Depacon studies with the much slower infusion rates included in Table 1 of the current Depacon labeling (somnolence 1.7%; paresthesias 0.9%).

Table 12.2b Summary of Most Frequently Reported[a] Treatment-Emergent Adverse Events

	Depacon® Treatment Group n (%)									
	1.5 mg/kg/minute (N = 40)					3.0 mg/kg/minute (N = 72)				
	Relationship				Total	Relationship				Total
COSTART Term	NR	PN	PO	PR	n (%)	NR	PN	PO	PR	n (%)
Somnolence	0	1	1	4	6 (15%)	1	1	1	4	7 (10%)
Nausea	1	1	0	2	4 (10%)	3	1	1	1	6 (8%)
Dyspepsia	1	1	1	0	3 (8%)	0	1	0	0	1 (1%)
Dizziness	0	1	1	1	3 (8%)	0	2	1	4	7 (10%)
Asthenia	1	1	0	0	2 (5%)	1	2	2	1	6 (8%)
Paresthesia	1	0	0	1	2 (5%)	1	0	0	5	6 (8%)
Vomiting	1	0	0	1	2 (5%)	1	1	0	0	2 (3%)

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.
[a] Adverse events occurring in ≥5.0% of subjects in either treatment group.

The Sponsor reports that the overall incidence of treatment-emergent adverse events was similar between the 1.5 mg/kg/min and the 3.0 mg/kg/min treatment groups (43% and 51%, respectively). The Sponsor reports that no statistically significant differences were detected between the two groups with respect to the incidence of any treatment-emergent adverse event associated with any body system or with respect to the incidence of any specific COSTART-coded adverse event.

Table 12.3a lists the three serious adverse events occurring during the study.

Table 12.3a Subjects Reporting One or More Serious[a] Adverse Events During the Study

Investigator/ Subject Number	Age (yrs)/ Gender	Day of Onset[b]	Length (days)	COSTART Term - Reason Serious	Relationship to Study Drug
Depacon® 1.5 mg/kg/minute					
Ramsay/703	59/ Female	8 (7)	4 hr 15 min.	Dyspnea - death, hospitalization, life-threatening	Unrelated
		8 (7)	4 hr 15 min.	Stupor - death, hospitalization, life-threatening	Unrelated
Depacon® 3.0 mg/kg/minute					
Cloyd/302	47/Male	5 (4)	4	Encephalopathy - hospitalization	Possible
Naritoku/209	26/Male	7 (6)	8	Hostility - hospitalization	Unrelated
		7 (6)	8	Drug level increased - hospitalization	Unrelated
		7 (6)	8	Confusion - hospitalization	Unrelated

[a] Defined as a fatal or life-threatening event, hospitalization, prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly, or required medical or surgical intervention to prevent regulatorily serious outcome.
[b] Number in parentheses represents the number of days following the last dose of study drug.

I have reviewed the safety reports of these three patients (Sections 12.3.1.1, 12.3.1.2, and 14.3.3) which I summarize as follows.

Patient 703 was a 59-year-old woman with a history of diabetes mellitus type 2 and breast cancer with metastasis to the brain. She had been hospitalized 3

days prior to receiving Depacon due to a generalized seizure. She had been given Decadron for control of mass effect of the metastases and Dilantin, Phenobarbital, and Depakote in an attempt to control seizures. She received the 1.5 mg/kg/min Depacon infusion. Radiation/oncology therapy was planned. On Study Day 8 (7 days after the infusion) she experienced gasping for air and unresponsiveness. Despite resuscitation efforts and transfer to the MICU, she died 4 hours later. The investigator considered the dyspnea, stupor, and death to be attributable to the brain metastases and not related to the study drug.

Patient 302, a 47-year-old man, received the 3-mg/kg/min Depacon infusion. On Study Day 5 (4 days post infusion) he awoke confused with slurred speech and was admitted to the hospital for evaluation. On oral Depakote, his ammonia level was 54 umol/L on Study Day 5 and 100 umol/L on Study Day 6. His Depakote was discontinued, and he was treated with Carnitor. His confusion and slurred speech resolved by Study Day 8. The investigator considered the hyperammonemia to be possibly related to study drug or, alternatively, to subsequent maintenance on oral valproic acid.

Patient 209, a 26-year-old man with past history of respiratory allergy and asthma, received the 3-mg/kg/min Depacon infusion. On study Day 7 (6 days post treatment), he was admitted for "severe violence and increased drug levels and moderate disorientation". On admission, he was on carbamazepine 2000 mg/day, lamotrigine 600 mg/day, and Depakote 3500 mg/day. On Study Day 7 his plasma valproate level was 145 ug/ml; the valproate level decreased to 63.8 ug/ml on Study Day 8. The levels of the comedications were not reported. He was treated with Ativan and Haloperidol, and his Depakote dose was reduced to 3000 mg/day. His symptoms had resolved by Study Day 14. The investigator considered the event to be unrelated to the study drug but attributable to Depakote toxicity.

Each of these serious adverse events occurred at a different site and was assessed by a different investigator. Based on the information presented, the investigators' assessments of the relation of Depacon to the events seem reasonable.

Hematology and Chemistry results were collected according to the protocol. A few subjects had values meeting the pre-defined limits of very high or very low values. I agree with the study report that these values do not appear to be clinically significant. A statistical comparison was made of the two infusion–rate groups. The only statistically significant difference observed was in change from baseline to the 1-week follow-up evaluation for BUN (mean change –1.5 mg/dl from a baseline of 14.3 mg/dL in the 1.5 mg/kg/min group; 1.5 mg/dL from a baseline of 13 mg/dL in the 3.0 mg/kg/min group). This minimal difference is not clinically significant.

According to the protocol, serum amylase determinations were part of the baseline and follow-up chemistry studies. No abnormal rises in serum amylase were detected including in patients with reported gastrointestinal adverse effects. Serum ammonia levels were not routinely determined as part of the baseline and follow-up chemistry studies. Serum ammonia was measured in patient 302 on Study day 5 only because he had become clinically encephalopathic as discussed in section 2.3 above.

Blood pressure measurements were recorded according to protocol. There were no statistically significant differences observed between the two infusion-rate groups with respect to the mean change from baseline measurement to the primary endpoints (to the 5-minute post infusion and to the minimum value following the first infusion in systolic and diastolic blood pressure). Table 12.5 a form the study report summarizes the mean change from baseline to each evaluation timepoint for systolic and diastolic blood pressure.

Table 12.5a Summary of Mean Changes From Baseline in Vital Signs Following First Infusion

	Depacon® Treatment Group				
	1.5 mg/kg/minute		3.0 mg/kg/minute		
Timepoint	N	Mean (SD)	N	Mean (SD)	P-value
Systolic Blood Pressure (mm Hg)					
Baseline	40	124.9 (17.53)	71	125.0 (15.66)	0.972
End of Infusion	39	126.1 (16.21)	67	126.0 (17.67)	
Change From Baseline	39	0.5 (10.79)	67	0.8 (10.70)	0.907
5 minutes Post-Infusion	38	125.6 (17.78)	64	124.2 (15.17)	
Change From Baseline	38	1.0 (9.99)	64	-1.6 (7.76)	0.153
10 minutes Post-Infusion	37	123.9 (14.86)	67	124.5 (15.84)	
Change From Baseline	37	-0.9 (12.05)	67	-0.8 (8.87)	0.967
20 minutes Post-Infusion	36	125.9 (15.94)	67	124.6 (15.33)	
Change From Baseline	36	0.8 (11.92)	67	-1.1 (11.45)	0.429
30 minutes Post-Infusion	38	126.3 (16.83)	68	124.1 (16.05)	
Change From Baseline	38	0.7 (11.77)	68	-1.3 (10.45)	0.388
Minimum Value	40	118.8 (14.60)	70	117.1 (15.83)	
Change From Baseline	40	-6.2 (9.02)	70	-8.2 (10.03)	0.291
Maximum Value	40	131.7 (16.17)	70	131.9 (15.53)	
Change From Baseline	40	6.8 (12.50)	70	6.6 (8.79)	0.939
Diastolic Blood Pressure (mm Hg)					
Baseline	40	75.3 (10.35)	71	71.9 (13.15)	0.171
End of Infusion	39	75.6 (10.89)	66	74.7 (14.72)	
Change From Baseline	39	0.0 (8.27)	66	2.1 (9.11)	0.236
5 minutes Post-Infusion	38	75.2 (10.53)	64	73.9 (14.27)	
Change From Baseline	38	-0.3 (8.41)	64	1.5 (8.06)	0.305
10 minutes Post-Infusion	37	75.2 (11.42)	67	71.5 (14.59)	
Change From Baseline	37	-0.5 (8.56)	67	-0.7 (8.05)	0.900
20 minutes Post-Infusion	36	72.8 (11.69)	67	73.1 (13.01)	
Change From Baseline	36	-2.7 (9.47)	67	0.9 (8.46)	0.049*
30 minutes Post-Infusion	38	74.0 (12.49)	68	72.7 (14.06)	
Change From Baseline	38	-1.3 (10.01)	68	0.6 (8.71)	0.292
Minimum Value	40	69.2 (11.76)	70	67.7 (13.43)	
Change From Baseline	40	-6.1 (9.10)	70	-4.4 (6.93)	0.300
Maximum Value	40	80.0 (10.54)	70	78.8 (13.20)	
Change From Baseline	40	4.7 (8.48)	70	6.6 (9.26)	0.299

* Statistically significant difference between treatment groups ($p \leq 0.05$).

Three subjects (all receiving the 3mg/kg/min rate) had a single blood pressure value, which met the predefined criteria of very low or very high values. This is summarized in Table 12.5b from the study report.

The study report notes that there was no placebo control in this study. Small changes in blood pressure occurred in the context of variable patient responses to infusion, venipuncture, etc. A simple linear regression analysis by the Sponsor, which used infusion rate as a continuous variable and vital sign change from baseline as the dependent variable, was used to assess whether the rate of infusion affected changes in blood pressure. The results indicated that the infusion rate is not affected by either the systolic or diastolic changes from baseline.

Table 12.5b Subjects With Vital Signs Values That Met the Criteria for Very Low or Very High Values

Investigator/ Subject Number	Age (yrs)/ Gender	Variable (units)	Baseline Value[a]	VL/VH		Final		VL/VH Criteria
				Value	Infusion Number[b]	Value	Day[c]	
Depacon® 3.0 mg/kg/minute								
Ramsay/719	64/Female	Diastolic Blood Pressure (mm Hg)	74	120 VH	1 (end of infusion)	88	9 (8)	≥ 105 mm Hg & increased ≥ 30 from baseline
Gates/109	39/Female	Systolic Blood Pressure (mm Hg)	115	83 VL	1 (30 minutes post infusion)	126	6 (5)	≤ 90 mm Hg & decreased ≥ 30 from baseline
Vazquez/803	36/Female	Systolic Blood Pressure (mm Hg)	105	74 VL	1 (end of infusion)	112	11 (10)	≤ 90 mm Hg & decreased ≥ 30 from baseline

VL = very low; VH = very high
a 5 minutes prior to first infusion.
b Evaluation point is indicated in parentheses.
c Numbers in parentheses are days after last dose of study drug.

2.4 Pharmacokinetic Results

Dr. Maria Sunzel of the Office of Clinical Pharmacology and Biopharmaceutics Review has written a detailed review of this study. She evaluated the following questions:

- *Is there a difference in the pharmacokinetics of valproate after an i.v. infusion at 3.0 mg/kg/min compared to 1.5 mg/kg/min (doses expressed as eq. valproic acid)?*
- *Are there any significant factors that affect the pharmacokinetics of valproate in epileptic patients after an i.v. infusion?*
- *Is it appropriate to initiate oral therapy (Depakote delayed release tablets) 1-3 h after stop of an i.v. infusion?*

Dr. Sunzel concluded that

1. *Depacon administered at infusion rates of 1.5 and 3.0 mg/kg/min over 10 and 5 minutes gave similar total valproic acid (VPA) plasma profiles, although early differences may not have been captured due to the chosen study design (1st plasma sample 15 min after infusion start). A Phase I study, where corresponding VPA infusion rates were given to healthy subjects, showed that total peak VPA concentrations (at infusion stop) were 26% higher after a 5-min infusion and 6% higher after a 10-min infusion, compared to the currently approved 60-min infusion. Two model simulations showed transiently higher free peak VPA concentrations (51% at the higher and 12% at the lower infusion rate compared to a 60-min infusion).*
2. *Concomitant treatment with anti-epileptic medications known to induce drug metabolism increased total and free clearance of valproate by 61% and 23%, respectively.*
3. *Initiation of oral therapy 1-3 h after stop of an i.v. infusion, is only recommended after a single i.v. infusion.*
4. *From a pharmacokinetic point of view, this supplemental NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Revisions of the proposed label are recommended.*

After reviewing the Sponsor's final report and discussing it with Dr. Sunzel, I made some additional observations.

The timing of the blood samples from the infusions did not permit a determination of the actual C-max for each group. However, the available AUC data indicated that the pharmacokinetics of valproate after the initial 15 mg/kg infusions were similar at the two rates (1.5 versus 3.0 mg/kg/min).

Near-peak total and free concentrations at 5 minutes after the infusions were completed were approximately 94.5 ug/ml and 14.3 ug/ml respectively. By 4-5 hours after the infusions, the concentrations of valproate had declined below 50 ug/ml.

The free (unbound) levels of valproate were determined using a commercial assay which require that blood samples not be stored for longer than a two week period. A comparison of the enrolled patient's study dates and the date of the assays suggest that most of the samples were stored for over three weeks; 22 of the patients' samples were stored for 15 weeks or more. The Sponsor has been asked for confirmation of this discrepancy and for any evidence that the stored sample would remain stable during this extended period of storage.

The Sponsor reports a trend for higher near-peak concentrations in uninduced patients with high body weights. The sponsor reports that preceding inducer use was a major explanatory variable in the concentration observed at the end of the study (6 hours) and in valproate clearance.

As discussed in previous sections, the infusions were clinically uneventful.

The Sponsor reports that pharmacokinetic/pharmacodynamic modeling failed to discern highly predictive relationships between pharmacokinetic variables and either blood pressure changes or the occurrence of other adverse events.

III. REVIEWER'S CONCLUSIONS

This study demonstrated the safety and tolerability of Depacon at an infusion rate of 3.0 mg/kg/min (which in a 70-kg adult would be about ten times the rate recommended in current labeling). However, the study was done in a relatively small number of patients who were selected to minimize possible adverse effects (e.g. no concomitant cardioactive medications and no history of hypotension, syncope, cardiac problems, etc). Therefore, it is not possible to generalize the finding of safety and tolerability to larger numbers of patients who might have one or more of such risk factors.

[redacted]

The current medical literature indicates that a higher infusion rate of Depacon has been used with some apparent efficacy for the treatment of status epilepticus, migraine status, and acute mania. Although the Sponsor is not asking for an indication for these entities in the labeling (which would require further safety and efficacy data), the inclusion of the higher infusion rates in the proposed labeling would likely be interpreted by practitioners as an endorsement of the use of Depacon in these patients. These types of patients may be at higher risk for adverse effects than were the patients in the current study due to their comorbid conditions or concomitant medications.

Some of the discussion in published case reports and series concerning the use of Depacon for the treatment of status epilepticus have speculated that Depacon might be less likely to cause sedation, arrhythmia, or hypotension in at-risk patients (elderly, concomitant medications, etc.) compared to intravenous phenytoin or fosphenytoin. This study does not include such patients so this speculation is not confirmed.

PK study results are incomplete due to the problems with the study design and the data collection discussed above. For example, true Cmax determinations

were not obtained. The unbound (free) levels were not consistently analyzed within the two-week timeframe recommended by the commercial assay used.

Baseline and post-infusion serum ammonia levels would be useful in determining if the rapid infusion increased the incidence of hyperammonemia associated with valproate. There are several small case series publications indicating that asymptomatic hyperammonemia of uncertain mechanism without evidence of hepatic dysfunction is common in patients on oral valproate especially if the patient is also on other antiepileptic drugs. Patients may become symptomatic if levels of ammonia rise high enough. There are published case reports of hyperammonemic encephalopathy after oral valproate overdose or when valproate is given to heterozygous carriers of ornithine transcarbamylase deficiency. There is a recent report (from the annual ADE report on 20-593) of a 52 year old man in status epilepticus who received intravenous Ativan and then was loaded with Depacon (quantity and rate of dose not specified); He was maintained on Depacon at 375 mg q 6 h. Within 10 hours of the Depacon loading dose, he slipped into deep coma with a slightly increased ammonia level (110) and slightly decreased carnitine levels. In this study, no preinfusion serum ammonia levels were determined, and post-infusion ammonia was determined on only one patient who had symptoms of hyperammonemic encephalopathy four days after the infusion while on Depakote maintenance therapy.

IV. RECOMMENDATIONS

[redacted]

An informational description of this study with appropriate discussion of its limitations could be incorporated into the labeling. Since all of the patients in this study received the 15 mg/kg-loading dose, the study description would appropriately be included on the labeling section discussing initiation of therapy rather than maintenance therapy.

[redacted]

V. COMMENTS TO THE SPONSOR

A teleconference with the Sponsor was held on April 27, 2001. The Sponsor agreed to review an approvable letter to be sent by the Division which will include suggested labeling changes describing this current study.

Philip Sheridan, M. D.
Medical Reviewer

4/30/01

NTL 4/30/01

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-593/SE2-006 AL**
Sponsor:	**Abbott Laboratories**
Drug:	**Depacon (Valproate Sodium Injection 500mg/5cc intravenously)**
[redacted]	
Material Submitted:	**Sponsor's proposed revisions to the Draft Labeling in the Division's May 3, 2001 Action Letter**
Correspondence Date:	**July 24, 2001**
Date Received / Agency:	**July 25, 2001**
Date Review Completed	**January 15, 2002**
Reviewer:	**Philip H. Sheridan, M.D.**

I. SUMMARY

This amendment to supplement S-006 is the Sponsor's counter-proposal of draft labeling submitted in response to the Division's May 3, 2001 Action Letter. The Sponsor has accepted most of the Division's proposed label revisions. [redacted]

[redacted] The Sponsor also proposes to revise the discussion of study M98-938 that studied the safety and pharmacokinetics of rapid IV infusions of Depacon.

This reviewer agrees with most of the minor editorial revisions and additions in this counter proposal. [redacted] Regarding study M98-938 of rapid infusions, [redacted]

[ ] Listing all adverse effects within [ ] of the infusion (regardless of whether or not they were deemed attributable to the Depacon) and also any adverse effects occurring later than [ ] which were felt to be attributable to Depacon would be acceptable.

II. BACKGROUND

The original NDA for intravenous sodium valproate (Depacon) was approved in 1996 (NDA 20-593).

The indication in current labeling for Depacon is as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

(1) Monotherapy and adjunctive therapy of patients with complex partial seizures in isolation or in association with other seizure types

(2) Sole and adjunctive therapy of patients with simple and complex absence seizures

(3) Adjunctive therapy of patients with multiple seizures types that include absence seizures.

Current labeling recommends administration of Depacon as a one-hour infusion at a rate not exceeding 20 mg/min. [For a 70-kg adult, this rate would be approximately 0.3 mg/kg/min.] Current labeling recommends that the intravenous doses be given at the same frequency (every 6 hours) as the oral valproate product (which it is temporarily replacing) although plasma monitoring and dosing adjustments may be necessary. It is not recommended for use over more than fourteen days.

The Sponsor submitted a Supplemental NDA (20-593/S006) based on Study M98-938, a Phase IIIB safety and tolerability study at infusion rates up to 3.0 mg/kg/min in epileptic patients. The Sponsor indicated that the intended purpose of study M98-938 was to provide data to support the rapid infusion of Depacon in clinical situations where the rapid attainment of steady state valproate levels in patients with low or absent serum levels is desired. The Sponsor stated that the study results were not intended to modify or expand on the currently approved indications. However, there are published reports in the medical literature about the use of valproate for status epilepticus (Sinha S and Naritoku DK , *Neurology*, 2000), migraine status (Norton J, *Headache*, Oct 2000), and the initial treatment of acute mania (Swann AC, *Am J Psych* 1999).

[ ]

The Division sent the Sponsor an Action letter (May 3, 2001) which proposed draft labeling changes including a description of the results of M98-938. [ ]

[ ]

This review addresses the Sponsor's current counter-proposal that accepts most of the Division's proposed label revisions. [ ]

[ ]

[ ] The Sponsor also proposes to revise the discussion of study M98-938 that studied the safety and pharmacokinetics of rapid IV infusions of Depacon.

III. REVIEW AND REVIEWER'S ASSESSMENT

The Sponsor in its submission of July 24, 2001 proposes the specific changes (revisions) below:

KEY TO REVISIONS:
TEXT = Proposed by FDA to be added and accepted by Abbott
~~TEXT~~ = Proposed by FDA to be deleted and accepted by Abbott
TEXT = Proposed by FDA to be added and rejected by Abbott
TEXT = Proposed by Abbott to be added in response to approvable letter.

Pharmacokinetics
Bioavailability

Eleven healthy volunteers were [ ] *given* single infusions of 1000 mg IV valproate over 5, 10, 30, and 60 minutes in a 4-period crossover study. Total valproate concentrations were measured; unbound concentrations were not measured. After the 5 minute infusions *(mean rate of 2.8 mg/kg/min)*, mean C_{max} was 145 ± 32 µg/mL, while after the 60 minute infusions, mean C_{max} was 115 ± 8 µg/mL. Ninety to 120 minutes after infusion initiation, total valproate concentrations were similar for all 4 rates of infusion.

Comment: Acceptable

Because protein binding is nonlinear at higher total [ ] *valproate* concentrations, the corresponding increase in unbound C_{max} at faster infusion rates will be greater.

Comment: Acceptable

[redacted]

[redacted]

ADVERSE REACTIONS

[redacted]

[redacted]

Comment:

The Sponsor has reduced the reported incidence of adverse effects from those in the May 3, 2001 Action letter. [redacted]

Table 12.2b from the final study report of M98-938 (reproduced below) shows the most frequently reported adverse events (i.e. AE's occurring in at least 5% in either treatment group.) These results were used to give the incidence figures used in the May 3 Action letter and include symptoms that patients reported in follow-up days after the infusion was completed. The investigators' assessment of the relation of the adverse effect to the drug is included in the table. The percent of patients experiencing the adverse events is approximately the same in each treatment group of M98-938. The adverse events and their incidence are also similar to what is reported in the current Depacon labeling for Depacon and Depakote. Table 2 in the current Depacon labeling indicates that patients on Depakote during a placebo control study reported a higher incidence of somnolence, dizziness, and gastrointestinal adverse effects compared to the Depacon studies in current labeling or study M98-938. Depakote patients did not report the paresthesias reported in the Depacon studies. Patients in the two groups of M98-938 had a five to six fold higher incidence of somnolence (15%, 10%) and paresthesias ((5%, 8%) compared to patients in the Depacon studies with the much slower infusion rates included in Table 1 of the current Depacon labeling (somnolence 1.7%; paresthesias 0.9%).

Table 12.2b Summary of Most Frequently Reported* Treatment-Emergent Adverse Events

	Depacon® Treatment Group n (%)									
	1.5 mg/kg/minute (N = 40)					3.0 mg/kg/minute (N = 72)				
	Relationship				Total	Relationship				Total
COSTART Term	NR	PN	PO	PR	n (%)	NR	PN	PO	PR	n (%)
Somnolence	0	1	1	4	6 (15%)	1	1	1	4	7 (10%)
Nausea	1	1	0	2	4 (10%)	3	1	1	1	6 (8%)
Dyspepsia	1	1	1	0	3 (8%)	0	1	0	0	1 (1%)
Dizziness	0	1	1	1	3 (8%)	0	2	1	4	7 (10%)
Asthenia	1	1	0	0	2 (5%)	1	2	2	1	6 (8%)
Paresthesia	1	0	0	1	2 (5%)	1	0	0	5	6 (8%)
Vomiting	1	0	0	1	2 (5%)	1	1	0	0	2 (3%)

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.
* Adverse events occurring in ≥5.0% of subjects in either treatment group.

[redacted]

After discussion, it was agreed that the Sponsor would submit the incidence of all the adverse effects up to [redacted] after the start of the infusion and any adverse effects felt by the investigators to be attributable to Depacon regardless of when they occurred.

On December 10, 2001, the Sponsor faxed AEs reported from the start of infusion to [redacted] after infusion and also any AEs deemed possibly or probably Depacon-related even if they occurred later than [redacted] after infusion. The common adverse events (>2%) were somnolence (10.7%), dizziness (7.1%), paresthesia (7.1%), asthenia (7.1%), nausea (6.3%) and headache (2.7%). In the opinion of this reviewer, this list is representative of the results of the study as reported in the M98-938 final study report.

Ammonia levels have not been systematically studied after I.V. valproate, so that an estimate of the incidence of hyperammonemia after I.V. DEPACON cannot be provided. Hyperammonemia with encephalopathy has been reported in 2 patients [redacted] after [redacted] infusions [redacted] of DEPACON [redacted]

Comment:

The Sponsor reviewed the results of M98-938 and found only one patient that had hyperammonemia with encephalopathy. Table 12.3a lists the three

serious adverse events occurring during the study, including this one patient.

Table 12.3a Subjects Reporting One or More Serious[a] Adverse Events During the Study

Investigator/ Subject Number	Age (yrs)/ Gender	Day of Onset[b]	Length (days)	COSTART Term - Reason Serious	Relationship to Study Drug
Depacon® 1.5 mg/kg/minute					
Ramsay/703	59/ Female	8 (7)	4 hr 15 min.	Dyspnea - death, hospitalization, life-threatening	Unrelated
		8 (7)	4 hr 15 min.	Stupor - death, hospitalization, life-threatening	Unrelated
Depacon® 3.0 mg/kg/minute					
Cloyd/302	47/Male	5 (4)	4	Encephalopathy - hospitalization	Possible
Naritoku/209	26/Male	7 (6)	8	Hostility - hospitalization	Unrelated
		7 (6)	8	Drug level increased - hospitalization	Unrelated
		7 (6)	8	Confusion - hospitalization	Unrelated

[a] Defined as a fatal or life-threatening event, hospitalization, prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly, or required medical or surgical intervention to prevent regulatorily serious outcome.
[b] Number in parentheses represents the number of days following the last dose of study drug.

Patient 302, a 47-year-old man, received the 3-mg/kg/min Depacon infusion. On Study Day 5 (4 days post infusion) he awoke confused with slurred speech and was admitted to the hospital for evaluation. On oral Depakote, his ammonia level was 54 umol/L on Study Day 5 and 100 umol/L on Study Day 6. His Depakote was discontinued, and he was treated with Carnitor. His confusion and slurred speech resolved by Study Day 8. The investigator considered the hyperammonemia to be possibly related to study drug or, alternatively, to subsequent maintenance on oral valproic acid.

The Action letter of May 3, 2001 draft labeling reports two patients because of a MedWatch report (99P1630060602-00) included in the annual ADE report on NDA 20-593. The report describes a 52 year old woman in status epilepticus who received intravenous Ativan and then was loaded with Depacon (quantity and rate of dose not specified); She was maintained on Depacon at 375 mg q 6 h. Within 10 hours of the Depacon loading dose, she slipped into deep coma with a slightly increased ammonia level (110) and slightly decreased carnitine levels. In this study, no preinfusion serum ammonia levels were determined, and post-infusion ammonia was determined on only one patient who had symptoms of hyperammonemic encephalopathy four days after the infusion while on Depakote maintenance therapy.

After discussion, the Sponsor has agreed to include both patients in labeling but has proposed changing [redacted] to [redacted] since the rate given the 52-yer old woman is not reported. This change is acceptable to this reviewer.

IV. REVIEWER'S CONCLUSIONS

Overall, the Sponsor's counterproposal for draft labeling does not differ greatly from the May 3, 2001 Action letter version. Further discussion with the Sponsor has narrowed the difference even further.

Most of the minor editorial revisions and additions proposed by the Sponsor in its counterproposal are acceptable.

[redacted]

The Sponsor has responded to the Division's concerns about its [redacted] the reported adverse effects observed in study M98-938 to [redacted] its reporting to include all adverse effects in the first [redacted] after infusion (regardless of whether or not they were deemed attributable to the Depacon) and also to include any adverse effects occurring later than [redacted] but felt to be attributable to the Depacon infusion. This approach gives figures that, in the opinion of this reviewer, are representative of the outcome of the study.

Study M98-938 demonstrated the safety and tolerability of Depacon at infusion rates up to 3.0 mg/kg/min (which in a 70-kg adult would be about ten times the rate recommended in current labeling). However, the study was done in a relatively small number of patients who were selected to minimize possible adverse effects (e.g. no concomitant cardioactive medications and no history of hypotension, syncope, cardiac problems, etc). Therefore, it is not possible to generalize the finding of safety and tolerability to larger numbers of patients who might have one or more of such risk factors.

However, practitioners who would be sophisticated enough to take the time to read about Study M98-938 in the labeling would probably realize that such studies usually enroll relatively healthy epileptic patients and don't necessarily represent the specific patient populations that these practitioners might be treating.

Philip Sheridan, M. D.
Medical Reviewer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Philip Sheridan
1/22/02 11:06:31 AM
MEDICAL OFFICER

John Feeney
1/22/02 04:54:45 PM
MEDICAL OFFICER
concur

MEMORANDUM

NDA 20-593/S-006 Depacon (valproate sodium injection)

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

SUBJECT: [redacted]

DATE: April 20, 2001

Depacon is currently indicated as an IV alternative in patients for whom oral administration of valproate products is temporarily not feasible. Depacon was approved based on the demonstrated bioequivalence of a 250mg dose of Depakote and a 250mg dose of Depacon *when the Depacon was administered as a one hour infusion.* Labeling notes that bioequivalence can be assumed for Depacon and Depakote up to the maximum recommended daily dose of Depakote (60mg/kg/day) because the kinetics of unbound valproate are linear.

The use of Depacon can be divided into 2 broad categories (as described in current Dosage and Administration). The first use is for initial exposure to valproate when oral administration is not feasible. The second use is for replacement therapy when oral administration is not feasible.

Initial Exposure

For initial exposure to Depacon, labeling advises a dose of 10 to 15 mg/kg/day in [redacted]

The original NDA for Depacon included some limited experience with larger and more rapid initial infusions of Depacon, but this experience is only briefly mentioned in the Adverse Reactions section in current labeling. Subsequent to its approval, Depacon has been administered off-label as an IV loading dose, with larger doses at more rapid infusion rates. There are numerous publications describing such experience. Certainly more rapid infusions are easier to administer. Whether the more rapid attainment of higher plasma levels has therapeutic benefit is less certain.

Current labeling for valproate products states, "The therapeutic range in epilepsy is commonly considered to be 50 to 100microgms/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations." If a therapeutic range was established, it follows that, once a decision was made to initiate therapy with valproate, the sooner those levels could be safely achieved, the better.

However, a therapeutic range has not been firmly established for valproate. Despite the common belief that 50-100 provides better seizure control than perhaps 30-50, I am not aware of prospective, randomized data that would support that contention. And in the current submission, the sponsor does not claim to demonstrate the superior efficacy of IV loading of Depacon over traditional dose initiation. Nevertheless, the division agreed with the sponsor in the past that if a large cohort of patients was treated at more rapid infusion rates, the safety experience of that cohort could be provided in labeling.

Replacement Therapy

In previous discussion with the sponsor, the division raised 2 concerns with more rapid infusions of Depacon for replacement therapy. First, changing from a 1 hour infusion to a 5 minute infusion could result in remarkably higher peak total plasma levels. These could increase risk to the patient. This risk might be compounded because the free fraction of VPA increases at high total plasma concentrations. Second, more rapid infusions could potentially result in lower trough levels between doses, causing a loss of efficacy.

The sponsor has provided PK data and safety data to address our concerns about the higher peak levels. However, none of the experience with rapid infusions actually occurred in patients receiving Depacon as replacement therapy. In Study 938 described later in this review, most patients had no measurable plasma concentrations of VPA at entry and the rest had very low levels. For replacement therapy, patients could theoretically have high plasma concentrations of VPA before switching to IV Depacon; the peak levels could theoretically exceed those seen in Study 938.

The sponsor has provided PK data to address our concerns about the lower trough levels.

Dr. Philip Sheridan has performed the primary clinical review of this application. Dr. Maria Sunzel was the primary biopharmaceutics reviewer.

Safety

Current labeling already includes limited safety data from more rapid infusions and IV loading doses of Depacon. The Adverse Reactions section states, "Dizziness and injection site pain were observed more frequently at a 100mg/min infusion rate than at rates up to 33mg/min. At a 200mg/min rate, dizziness and taste perversion occurred more frequently than at a 100mg/min rate. The maximum rate of infusion studied was 200mg/min." These statements were based on only small numbers of patients.

The primary study in this submission is Study 938. This was a randomized, open-label parallel study of 2 infusion rates of Depacon. Patients who were deemed in need of a rapid infusion of Depacon were randomized to receive an IV loading dose at either

1.5mg/kg/min (10 minute infusion) or 3.0mg/kg/min (5 minute infusion). It was a 1:2 randomization so that 37 were in the 1.5 group and 75 were in the 3.0 group. Patients were entered who required either initial therapy or who had low levels of VPA (<50). For initial therapy, the dose was 15mg/kg. A formula was provided to compute the dose for patients with a low level of VPA.

Patients could be using concomitant antiepileptic drugs. Patients could be 2 years of age or older. Patients with status epilepticus were excluded.

After IV loading, patients had a total VPA level checked at 1 hour. If the level was below 50, another IV dose could be given, again using the provided formula. Patients were followed for a total of 6 hours and serial blood samples were collected for PK analysis. Oral dosing was not allowed during this 6 hour period.

Roughly half of all patients who were enrolled were being exposed to valproate for the first time; all patients received a 15mg/kg dose. Only 2 patients received a second IV dose of Depacon during the first day of the trial. Therefore, the bulk of experience was with a single IV loading dose in VPA-naïve patients.

There was some overlap between assigned groups in the actual infusion rates received. Because of this the sponsor proposes re-assigning some patients to the alternative group for between-group analyses.

There was one death in the study, 7 days after the infusion, in a woman with metastatic breast cancer. There is nothing to indicate a relationship to study drug.

There were 2 other serious adverse events. A 47 year old man developed elevated ammonia, slurred speech, and confusion 4 days after receiving a 3mg/kg/min Depacon infusion followed by maintenance therapy with oral Depakote. Oral Depakote was stopped and he recovered. A 26 year old man developed violent behavior and disorientation 6 days after a 3mg/kg/min Depacon infusion followed by maintenance therapy with oral Depakote. At the time of admission, he was on extremely high doses of Depakote, Lamictal, and carbamazepine. His VPA level was 145 which was felt to explain his clinical status. He improved over 1 week with lowering of his Depakote dose and treatment with Haldol and Ativan.

Common adverse events seen were somnolence (12%), nausea (9%), dizziness (9%), paresthesia (7%), asthenia (7%), and vomiting (4%). In the original NDA for Depacon, the incidence of these same events were: somnolence (2%), nausea (3%), dizziness (5%), paresthesia (1%), asthenia (0%), and vomiting (1%). A direct comparison between the NDA cohort and Study 938 could or course be confounded by the circumstances of the trials and the types of patients enrolled.

Dr. Sheridan's review did not identify any significant laboratory or vital sign abnormalities. Because of the known risk of pancreatitis with VPA, amylase levels were routinely monitored; there were no abnormal amylase levels reported.

No clear differences were seen between the 2 treatment groups in Study 938. Given that the infusion rates for both treatment groups in Study 938 were an order of magnitude above the currently approved rate, the comparison of interest may be the pooled groups from Study 938 versus the safety cohort described in current labeling.

Pharmacokinetics After Rapid IV Infusions

Study 938

By protocol, free and total plasma levels were not collected until well after the end of the Depacon infusions. Therefore, this study does not contribute greatly to our understanding of peak levels and to the free fractions at those peak levels.

Study 182 (Previously submitted in Original NDA)

Eleven subjects in this Phase 1 study received 1000mg over 5, 10, 30, or 60 minutes in a 4-period crossover study. Only total VPA levels were determined in this study. The concentration-time profile on page 7 of Dr. Sunzel's review demonstrates that total levels of VPA after the faster infusions do transiently exceed those seen after the 60 minute infusion. However, the overshoot is less than might be expected given the 10-fold increase in rate.

The same concentration-time profile demonstrates that, after 90-120 minutes, the total VPA levels follow almost the same pattern, thereby addressing our concern about lower trough levels with faster infusions.

Study 197 (Previously submitted in Original NDA)

This Phase 1 study evaluated the PK and safety after an IV loading dose of 1000mg Depacon infused over 10 minutes, followed by oral Depakote maintenance dosing which differed among 3 randomized groups. Fifteen normal volunteers received the IV load followed by oral Depakote, 500mg q 8hrs with the first oral dose at 1 hour; 15 volunteers received the same IV load followed by oral Depakote, 500mg q 8hrs with the first oral dose at 3 hours; and 15 volunteers received the same IV load followed by oral Depakote, 250mg q 6hrs with the first dose at 1 hour.

Total VPA levels were collected throughout the study.

Peak total VPA concentrations after the 10 minute infusions were in agreement with those seen in Study 182.

PK Analyses of Study 938

Dr. Sunzel has reviewed these analyses. The main limitation to these analyses was that free and total levels were not obtained until after the end of the infusions. In addition, because of the time that elapsed before free concentrations were actually determined in the samples drawn, the reliability of the results is in question. Dr. Sunzel has tried to validate the results obtained by comparing results to previous experience. See her review for the details of this exercise.

Dr. Sunzel has also provided simulations of free VPA levels after rapid infusions. These simulations suggest that free VPA levels may be 50% higher after a 5 minute infusion compared to a 60 minute infusion.

Pharmacokinetics After IV Loading and Subsequent Oral Maintenance Dosing

The optimal timing of oral maintenance therapy after IV loading has been addressed to some extent by the sponsor. The timing can be considered "optimal" only in the sense that plasma levels of 50-100, the commonly accepted therapeutic range, are best maintained. In Study 197, the sponsor investigated the effects of varying the initiation of oral maintenance from 1 to 3 hours post infusion. The 45 volunteers in this study had safe passage and achieved reasonable plasma levels. The plasma levels achieved are shown on page 8 of Dr. Sunzel's review. The trough levels after the second oral dose were generally between 40-50.

DSI Issues

A number of issues were raised during inspections of one of the clinical sites, Site 7, in Study 938 and an analytical site.

The analytical site inspection revealed that, while validation studies indicated certain plasma levels should be analyzed within a few weeks, samples were left as long as 6 weeks before being analyzed. There were other violations of the protocols. However, because the PK results from Study 938 do not contribute greatly to our understanding of more rapid infusions (due to the late timing of total and free samples), this particular flaw does not affect the application.

At Site 7, it was found that the drug was administered manually, rather than with an infusion pump. The DSI review questions whether a constant infusion rate could be maintained without the use of an infusion pump. The durations for total infusions were generally in the range of 5-10 minutes. I believe this would have been a more important problem if a rigorous comparison of the 1.5 rate and the 3.0 rate was contemplated for labeling. However, if the randomized rate groups are pooled together and the pooled experience treated as open, uncontrolled data, this deviation from protocol seems less important. Infusion rates could probably not have been constant for patients given the

drug manually. The DSI report suggests asking the sponsor whether manual delivery occurred at other sites.

Although the protocol was later amended to allow for smaller dilution volumes, Site 7 began using smaller dilution volumes before the amendment was approved.

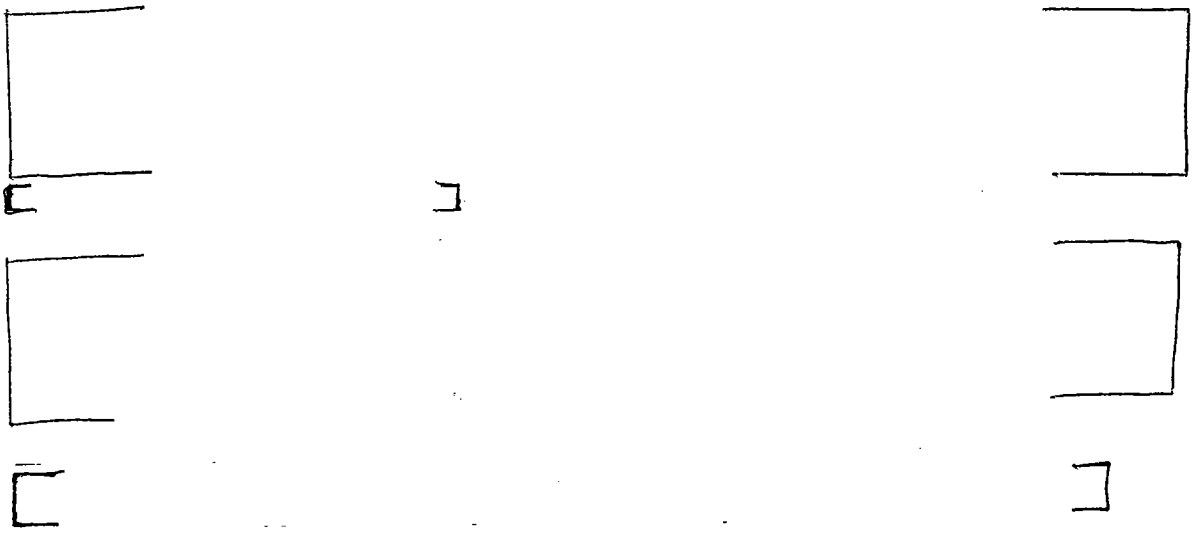
There were some random errors in informed consent procedures, to include using an English version for a Spanish-speaking patient. Apparently, the patients were informed verbally in Spanish.

Miscellaneous record-keeping/documentation problems were also noted, but seem of minor import overall.

There were some random protocol violations regarding inclusion/exclusion criteria.

Conclusions

Based on the accumulated experience described above, the sponsor should be sent an Approvable Letter with labeling to be negotiated in the near future.



Final labeling must incorporate these facts into the appropriate sections of labeling.

In the Approvable Letter, the sponsor should be asked whether manual drug delivery (as opposed to the use of infusion pumps) occurred at sites other than Site 7. I do not believe the other issues uncovered by DSI need to be addressed in the Approvable Letter.

Appears This Way
On Original

cc: NDA 20-593
Katz/Feeney/Sheridan/Ware/Fanari

MEMORANDUM

NDA 20-593 Depacon (valproate sodium injection)
S-006

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

SUBJECT: Response to Approvable Letter

DATE: January 15, 2002

In a Prior Approval Supplement dated June 30, 2000, the sponsor had proposed changes to labeling describing the experience with more rapid infusions of Depacon than those provided for in current labeling. Depacon was originally approved based on bioequivalence with oral Depakote. The bioequivalence was demonstrated when Depacon was administered over 60 minutes.

In the supplement, the sponsor proposed including descriptions of the safety experience accumulated with infusions 5-10 fold faster than described in labeling. [redacted]

In the Approvable Letter and accompanying draft labeling, DNDP [redacted]

In the Response to the Approvable Letter, the sponsor re-visited some of these same areas without any new substantive arguments. Additional minor editorial changes and changes to adverse event tabulations were submitted and are all discussed in Dr. Sheridan's medical review. Dr. Sunzel has also provided a biopharmaceutics review.

After discussions with the sponsor, labeling acceptable to the sponsor and DNDP was developed. This labeling does not differ substantively from the draft labeling which accompanied the Approvable Letter.

Conclusions

The sponsor should be sent an Approval Letter with the labeling developed with the sponsor.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Feeney
1/15/02 04:37:43 PM
MEDICAL OFFICER

MEMORANDUM

DATE: April 26, 2001

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

TO: File, NDA 20-593/S-006

SUBJECT: Action Memo for NDA 20-593/S-006, for the use of Depacon at increased rates of infusion

Depacon is an injectable form of valproic acid approved for temporary use as substitution for oral valproate products in the treatment of seizures. It is currently approved for use at a maximum daily dose of 60 mg/kg, and is to be given in the same milligram amount as an oral dose, as a 60 minute infusion, with the maximum rate to be no more than 20 mg/minute. The original approval of the product was based on the sponsor's showing that a given dose of Depacon given as a 60 minute infusion was bioequivalent to that dose when given orally.

On June 30, 2000, Abbott Laboratories submitted this supplement, the intention of which is to add statements in labeling describing [ ] infusion rates of up to 3 mg/kg/minute, which is approximately 10 times that currently approved as the maximum rate of infusion (for a 60 kg person). The application includes a report of Study M98-938, in which 112 patients were randomized to receive a 15 mg/kg dose of Depacon over 5 or 10 minutes. The purpose of this study was to demonstrate that these greater infusion rates are well tolerated. In addition, the sponsor re-submitted 2 studies from the original submission: Study F90-182, in which 16 healthy male volunteers received a 1000 mg eq. Valproate injection given over 5, 10, 30, and 60 minutes, and Study F90-197, in which 45 healthy volunteers received this dose in a 10 minute infusion, followed by various regimens of oral dosing.

The application has been reviewed by Dr. Philip Sheridan, medical officer (review dated 4/11/01), Drs. Maria Sunzel and Elena Mishina, Office of Clinical Pharmacology and Biopharmaceutics (review dated 4/17/01), Mr. Donald Schuirmann, Quantitative Methods and Research Staff, and Dr. John Feeney, Neurology Team Leader (review dated 4/20/01). In this memo, I will briefly describe the results of these studies and analyses, and offer support for the division's action on this supplement.

STUDY F90-182

This was a cross-over study in 23 healthy males, in which 16 received drug and 7 received placebo. Of the 16 who received drug, data from 11 were included in the pharmacokinetic (PK) analyses.

These subjects received a dose of 1000 mg eq valproic acid given over 5, 10, 30, and 60 minutes, each infusion separated by a 7 day washout period. These infusions correspond to rates of about 3, 1.5, 0.5, and 0.25 mg/kg/minute. The following parameters were obtained for total VPA concentrations:

	3 m/k/m	1.5 m/k/m	0.5 m/k/m	0.25 m/k/m
Cmax	145	122	137	114
Tmax (hr)	0.2	0.22	0.54	1.08
AUC(0-72)	1798	1587	1576	1546
T ½ (hr)	15.9	15.5	16.3	15.9

As noted above, these values represent total VPA levels. The sponsor and the OCPB reviewers simulated free VPA levels at Cmax (end of the infusion). The following results were computed:

	3 m/k/m	1.5 m/k/m	0.25 m/k/m
Cmax	29	22	19

The Cmax after the 3 mg/kg/min infusion was about 1.5 that after the 0.25 mg/kg/min infusion (the latter rate corresponds to a dose of 1000 mg given according to the currently recommended 60 minute infusion).

STUDY F90-197

In this study, 15 healthy male volunteers received one of 3 dosing regimens: each received 1000 mg eq valproate in a 10 minute infusion, followed by one of the following oral dosing regimens: 500 mg q8h, starting 1 hour after the start of the 10 minute infusion; 500 mg q8h, starting 3 hours after the start of the infusion; and 250 mg q6h, starting 1 hour after the start of the infusion. Each subject received oral dosing for 3 days. The following chart displays the data after the first oral dose:

	500 q8h 1 hour	500 q8h 3 hour	250 q6h
Cmax	105	81	69
AUC	642	530	473
Cmin	61	54	63

Steady state Cmin appeared to have been achieved by 24 hours after the initial infusion.

The values after the second dose were somewhat lower than those displayed above.

In this study, VPA levels were measured at the end of the infusion (Cmax); they ranged from 95-113, values which were comparable to, though somewhat less than, those seen after the 10 minute infusion in Study F90-182.

STUDY M98-938

In this study, 112 patients with low (<50 mcg/mL) or undetectable valproate levels were randomized (2:1) to receive a 15 mg/kg dose given in a 3 mg/kg/min (5 minute) or 1.5 mg/kg/minute (10 minute) infusion. Although the protocol permitted multiple infusions, essentially all patients received only 1 infusion. In this study, total and free VPA levels were measured.

Various modeling procedures were applied to the data, including [redacted] analyses. Unfortunately, the protocol did not call for sampling at Cmax (only at various times after the end of the infusion), so accurate assessments of Cmax could not be made.

There was a non-linear increase in free VPA concentrations in the range of 50-150 mcg/mL. Clearance of free VPA was about 23% greater in patients taking concomitant enzyme inducing AEDs compared to those who were taking non-enzyme inducing AEDs.

At 15 minutes after the start of the infusion, the total and free VPA levels were comparable between the 2 regimens.

Patients were monitored closely and frequently for vital sign and EKG changes; there were no changes of clinical importance.

An inspection of this study revealed that the sponsor did not analyze the stored frozen plasma samples for free VPA levels in the 2 week period of storage required by the method used (apparently, no such time limit is imposed for total VPA levels). The stability of the free VPA levels in frozen samples for greater than 2 weeks is unknown, and the sponsor has not submitted evidence that addresses this concern. For this reason, the free VPA level determinations in this study are suspect. To address this concern, predictions of free VPA levels using the total levels and protein binding data from a literature source were performed; they yielded predictions of free VPA levels that were extremely close to those observed in this study.

COMMENTS

The sponsor wishes to alter a number of sections of current labeling, in particular the Clinical Pharmacology, Adverse Reactions, and Dosage and Administration

sections. [redacted] (current labeling suggests that daily doses greater than 250 mg should be given in divided doses). They have not proposed changing the maximum daily dose (60 mg/kg). [redacted]

The sponsor has presented several sources of evidence, both clinical and pharmacokinetic, about infusion rates of up to 3 mg/kg/minute of Depacon, [redacted] The largest source of evidence, Study M98-938, exposed 112 patients to a dose of 15 m/k at rates of 1.5 mg/kg/minute (N=40) and 3 mg/kg (N=72). In this study, these doses and rates were reasonably well tolerated, although the effects of only one infusion/patient were assessed. Unfortunately, because of the study design, true Cmax levels were not obtained in this study.

Study F90-197 examined the kinetics (and tolerability) of various oral dosing regimens given after a 10 minute infusion of 1.5 mg/kg/minute, again, after only a single such infusion (a total of 45 healthy males received the infusion, with 15 each receiving a different oral regimen). Study F90-182 examined the kinetics and tolerability of single 1000 mg infusions given over 5, 10, 30, or 60 minutes in 16 healthy males.

[redacted]

A number of points need to be made.

First, the Cmax for total VPA concentrations seen after the 3 mg/kg/minute infusion is about 26% greater than that seen after the same dose given as a 60 minute infusion (from Study 90-182). This difference is not nearly so great as the percent increase in infusion rate it represents (which is 12 times that of the 60 minute infusion). However, the sponsor has presented no empirical data that adequately documents the true Cmax of **free** VPA. To address this deficiency, simulations have been performed, and it appears that Cmax for the 3 mg/kg/minute infusion is about 50% greater than that seen after the approved 60 minute infusion. Although this rate of infusion appears to have been relatively well tolerated in about 70 patients (and an additional 45 healthy male volunteers), the patients (and, of course, the healthy volunteers) were screened to exclude patients with significant systemic disease and, in particular, those taking

cardioactive drugs. [redacted] As noted earlier, the approval of the 60 minute infusion rate in current labeling was based on a showing of bioequivalence to oral dosing. As such, not only efficacy, but the safety of the original 60 minute infusion was based on the years of accumulated safety evidence with the oral product. Although the sponsor has, in my view, demonstrated the tolerability of the [redacted], as it were, with the rates currently approved, and which, again, are based on the years of experience with the exposures associated with the oral product.

[redacted]

Having said this, however, I do believe that we can include a statement in labeling that describes the experience with these new rates and doses. Specifically, I would be willing to permit a statement in the Dosage and Administration section of labeling that states that about 100 people with sub-therapeutic or non-detectable valproate levels have been treated with rates up to 3 mg/kg/min and single doses of 15 mg/kg and that these have been relatively well tolerated, although only single infusions have been studied, and the effectiveness of these rates compared to the infusion rate of 20 mg/min given over 60 minutes has not been studied.

[redacted]

[redacted]

Currently, labeling describes the conversion from oral dosing only for the 60 minute infusion, and states that a dose of Depacon should be treated as any other dose; i.e., it should be given at the same time that an oral dose would be given.

[redacted]

The sponsor also wishes to provide an [redacted] description of Study M98-938 in the Adverse Reactions section of labeling, [redacted]

[redacted]

[redacted] and I believe a simple statement listing the more common ADRs seen in Study M98-938, with accompanying language that because these data come from different studies they are not directly comparable, will suffice.

Finally, as Dr. Sunzel notes, DSI's audit revealed that we have no stability data for the frozen plasma samples used to measure free VPA levels in Study M98-938 beyond 2 weeks, although many of the samples were stored for longer than 2 weeks by the time the assay was performed. However, the measurement of free VPA levels in this study is not critical to our decision; as noted previously, true Cmax was not measured in this study, and so we are primarily relying on this study to provide safety data for the rapid infusion. For this reason, I would not

require that this stability data be in hand in order for a final action to be taken on this application.

Therefore, for the reasons stated above, I will issue the attached Approvable letter with attached draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
5/3/01 04:26:40 PM
MEDICAL OFFICER

MEMORANDUM

DATE: January 24, 2002

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

TO: File, NDA 20-593/S-006

SUBJECT: Action Memo for NDA 20-593/S-006, for the use of Depacon at increased rates of infusion

NDA 20-593/S-006, for the use of Depacon at increased rates of infusion, was submitted by Abbott Laboratories on 6/30/00. The application contained the results of studies examining the safety and kinetics of rates of infusion of Depacon substantially greater than those recommended in current labeling. The sponsor had proposed a number of labeling changes based on these data.

In an Approvable letter of 5/3/01, we rejected most of the proposed changes (for details, see my Action Memo dated 4/26/01). The sponsor responded to our letter in a submission dated 7/24/01. This response has been reviewed by Dr. Philip Sheridan, medical reviewer, Dr. John Feeney, Neurology Team Leader, and Dr. Maria Sunzel of the Office of Clinical Pharmacology and Biopharmaceutics.

While the sponsor agreed with a number of our arguments, [redacted] The review team has discussed these matters with the sponsor, and we have agreed to labeling that is, in all major aspects, similar to the labeling accompanying the Approvable letter and the currently approved label for Depacon, (e.g., most of the sponsor's originally proposed statements have not been adopted), although some minor changes have been made.

There is one additional issue that needs to be addressed.

In our Approvable letter of 5/3/01, we asked the sponsor to determine how the infusions were given in the 12 sites of Study M98-938 that were not investigated (results of the inspection of one site revealed that at that site, the infusion was given by hand, not by pump, and we questioned the appropriateness of this manner of infusion). The sponsor responded that the infusion was given by hand at only one other site. Therefore, only 26 of the 86 patients in the study did not receive the infusion by pump. This is acceptable.

For the reasons stated above, then, I will issue the attached Approval letter with appended labeling.

Russell Katz, M.D.

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/s/

Russell Katz
1/24/02 02:20:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

STATISTICAL REVIEW

Statistical Review: NDA 20-593/S-006, Depacon (valproate sodium injections), Abbott Laboratories

Material reviewed: Study report "The Safety and Tolerance of Intravenous Depacon® at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy" from NDA 20-593/S-006

The Sponsor carried out a study, described in the report "The Safety and Tolerance of Intravenous Depacon® at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy" (included in the Sponsor's submission). This was an open-label, prospective, randomized, Phase IIIB, parallel group, multi-center trial of intravenous Depacon® (valproic acid) in subjects with epilepsy. One hundred and twelve male and female subjects with epilepsy were randomized and treated in the study.

A number of statistical analyses were carried out, including analyses using [ ]. The subject of this review is the Sponsor's covariate analyses using SAS. For the responses log(Cmax) (observed Cmax from individual concentration-time profiles) and log(CL) (CL=clearance, post hoc estimates obtained from [ ]), for both free valproic acid (VPA) and total VPA, the report describes multiple regression models in which certain potential covariates – induction status, weight, age, albumin, gender, presence of lamotrigine, creatinine, and dosing rate - were examined as potential explanatory variables for the responses. Similarly for the response K_1 (protein binding constant, post hoc estimates from [ ] runs) induction status, cholesterol, creatinine, and age were considered as potential explanatory covariates. Elena V. Mishina, Ph.D. (pharmacometrics specialist in the Office of Clinical Pharmacology and Biopharmaceutics) requested an assessment of the appropriateness of the Sponsor's covariate analyses.

The Sponsor's covariate analyses examined the linear relationship between the response and the selected covariates. So long as it is appropriate to restrict attention to *linear* statistical models, use of SAS software such as SAS PROC GLM or SAS PROC REG, which utilizes small-sample test methods such as t-tests and F-tests, is as good as, and probably preferable to, nonlinear software such as [ ], which relies on large-sample, asymptotic methods such as likelihood ratio tests and Wald tests. Whether or not *nonlinear* models should have been considered for any of the potential covariates examined is beyond the scope of this review.

The problem faced by the Sponsor is described in the statistics literature as "selecting the 'best' regression." Various statistical methods have been proposed over the years for deciding which covariates to select, out of a pool of candidate covariates, which best achieve a balance between including covariates that improve the predictive power of the final regression model and not selecting covariates that produce little or no improvement in predictive power, producing the most parsimonious final model possible. Speaking about this statistical problem, Draper and Smith wrote:

> There is no unique statistical procedure for doing this, and personal judgment will be a necessary part of any of the statistical methods discussed.

(Draper, N.R., & Smith, H. (1966) **Applied Regression Analysis**, John Wiley & Sons, Inc., New York, 407pp.) The point is that there is no universally recognized "best" method for covariate selection.

A number of methods have been proposed over the years, most notably Forward Selection, Backward Elimination, Stepwise Regression, and Stagewise Regression. Descriptions of these methods may be found, for example, in standard texts such as Draper and Smith, or in the SAS documentation for PROC REG (in a volume such as SAS Institute Inc. *SAS/STAT™ User's Guide, Release 6.03 Edition.* Cary, NC: SAS Institute Inc., 1988. 1028pp.)

Based on the Sponsor's report, it was not clear what method of covariate selection was used. A telephone conversation was held at the request of Dr. Mishina. (See my memorandum of telephone conversation, attached to this review.) Based on this conversation it was apparent that the Sponsor used a version of the Forward Selection method. In this method, covariates are added to the model one at a time, based on which covariate provides the most statistically significant improvement to the fit of the model. Once the first covariate is chosen, other covariates are considered for inclusion in the model based on the improvement of fit they produce in a model that includes the first covariate selected. Covariates are sequentially added to the model in this fashion until none of the remaining covariates give a statistically significant improvement to the fit of the model (the Sponsor used a level of significance of 0.10.) In this case, the Sponsor forced one covariate, induction status, to be in all of the regression models, regardless of statistical significance. This was done for physiologic reasons.

It appears that the analysis of variance tables for the models finally selected are contained in Appendix D of the report. Based on those tables, the covariates selected were:

ln(Cmax) total VPA	induction status, weight, albumin, dosing rate
ln(Cmax) free VPA	induction status, weight, age, dosing rate
ln(CL) total VPA	induction status, weight
ln(CL) free VPA	induction status, weight, age, dosing rate
K_1	induction status, age

This list of covariates selected for each response is somewhat inconsistent with the Results and Discussion section of the Sponsor's report. Under the subheadings Predictors of C_{max} and Clearance:, C_{max}:, the report states "In this analysis, effects for previous experience with inducers, use of lamotrigine in the 3 days preceding study drug administration, weight and gender were not statistically significant ($p>0.1$)." This is true for Cmax both for total and free VPA, and yet in both cases induction status and weight were included in the final regression model (It is a feature of the Forward Selection method that a covariate may be entered into the model, and thus its contribution to the model is statistically significant when it enters, but then other covariates added

subsequently can make the contribution of covariates added earlier non-significant. This was the case for weight in both the total VPA and the free VPA ln(Cmax) analyses.) In the case of Clearance, the report states "In this analysis, effects for age, albumin, gender, presence of lamotrigine, creatinine and dosing rate were not statistically significant ($p>0.1$)." But in the analysis of variance table for ln(CL) for free VPA (Appendix D.2, page number 207 at the bottom of the page), the p-values for age and dosing rate are given as 0.0738 and 0.0665 respectively. This discrepancy is not explained.

The study was a multi-center trial, but the Sponsor presents no analyses designed to determine if the effects of covariates depend on the specific center.

Summary

1. The Sponsor's covariate analyses only considered linear relationships between covariates and response. This is not uncommon in exploratory analyses, since even nonlinear relationships might be expected to have a linear component. Nevertheless, the question of whether nonlinear models should have been considered for one or more of the candidate covariates is beyond the scope of this review.

2. Given that only linear relationships were considered, use of SAS procedures, such as SAS PROC GLM and SAS PROC REG, is appropriate.

3. The Sponsor appears to have used a version of the Forward Selection method of covariate selection (see attached memorandum of telephone conversation.) Other selection methods are available, but the Forward Selection method is well established, and no selection method has been identified as the "best" method to use. The Sponsor's choice, therefore, seems reasonable.

4. There is some inconsistency between the Sponsor's selected covariates, as given in Appendix D. of the report, and their Results and Discussion section. In particular, for ln(CL) of free VPA the effects of age and dosing rate are described as "not statistically significant ($p>0.1$)" in the Results and Discussion section of the report, but in Appendix D. the p-values are given as 0.0738 for age and 0.0665 for dosing rate.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods and Research Staff (HFD-705)

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:
Original NDA 20-593/S-006
HFD-860 Elena V. Mishina
HFD-860 Emmanuel Fadiran
HFD-705 Stella G. Machado
HFD-705 Donald J. Schuirmann
HFD-705 QMR Chron

Attachment - Memorandum of 12/21/00 Telephone Conversation

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Memorandum of Telephone Conversation

December 21, 2000 - 3:15pm to 3:38pm

between: representatives of Abbott Laboratories:
Steve Townsend (regulatory affairs)
Charles Locke (statistician)
Yi Ming Zhang (statistician)

and: Donald J. Schuirmann, Expert Mathematical Statistician, QMR Staff (HFD-705)

Subject: NDA 20-593/S-006 (Depacon)

The telephone conversation was held at the request of Elena V. Mishina, Ph.D. of the Office of Clinical Pharmacology and Biopharmaceutics. The subject was the method used for covariate selection in the analysis of a study of intravenous Depacon (valproate sodium injection) infusion rates, reported in NDA 20-593/S-006.

The report describes multiple regression models in which certain covariates – induction status, weight, age, albumin, gender, presence of lamotrigine, creatinine, and dosing rate - were examined to see if they were predictors of certain responses – the logarithms of observed Cmax for free valproic acid (VPA), observed Cmax for total VPA, Clearance (post hoc estimates from ⊏ ⊐ runs) for free VPA, and Clearance for total VPA. Similar analyses were carried out for the response K_1 (protein binding constant, post hoc estimates from ⊏ ⊐) using induction status, cholesterol, creatinine, and age as potential covariates. I said that it was not clear from the study report how the firm had decided which covariates to include in the regression models. I noted that a rather long series of SAS statements had been provided by the firm, but that I could not determine the covariate selection method from examining these SAS statements.

Dr. Zhang indicated that they had tried using classic stepwise regression as implemented in SAS PROC REG, but that they were not satisfied with the resulting set of covariates on physiological grounds, based on consultation with other scientists at the firm. In particular, it was felt that induction status should be included in the regression models on physiological grounds. The firm decided to use the following strategy:

1. Candidate covariates were tried, one at a time, in a regression model that was forced to include induction status. If the improvement in the fit of the model was statistically significant (at the 0.10 level of significance) for a particular covariate, that covariate was added to the model.

2. Once a covariate was placed in the model, it stayed in the model. Subsequent candidate covariates were then tried in a model including any previously entered covariates.

3. Selection ceased when none of the remaining candidate covariates produced a statistically significant improvement in the model.

As stated in #2., once a covariate was entered into the model, it stayed in the model. This explains, for example, why in the final regression model for log Cmax for Total VPA (see Appendix D.1, APPENDIX PAGE 1, NDA 20-593/S-006 Vol 2 Pg 204) the p-value for the weight covariate is non-significant (p=0.1532). When weight was initially added to a model that had only induction status, it was significant, and so it was added to the model. When albumin and dosing rate were subsequently added to the model, weight was no longer significant, but was not removed.

The covariate selection method described by the firm appears to be a version of the *Forward* selection method, as implemented in SAS PROC REG. In the telephone conversation I did not determine whether the firm used SAS PROC REG, or whether they did the calculations "by hand". Dr. Zhang indicated that formal use of the *Stepwise* selection procedure, with induction status forced into the model, produced models very much like the ones reported. The firm did indicate that the long series of SAS statements, which make frequent calls to SAS PROC GLM, was used to produce display Analysis of Variance tables for inclusion in the study report, not to do the actual model selection.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods and Research Staff
Office of Biostatistics, CDER

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/s/

Donald Schuirmann
3/6/01 04:14:23 PM
BIOMETRICS

for concurrence

Stella Machado
5/17/02 05:27:28 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Valproate sodium (Depacon® Injection for intravenous use), eq. 100 mg/mL valproic acid

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

NDA 20-593/S-006

Submission Dates:	Jun. 30, Sept. 15, Nov. 14, 2000; Jan. 19, Apr. 12, 2001
Primary Reviewer:	Maria Sunzel, Ph.D.
Pharmacometric Reviewers:	Elena Mishina, Ph.D.
	Donald Schuirmann, Expert Mathematical Statistician

Indication: Monotherapy or adjunctive therapy of patients with seizures (anti-epileptic)

EXECUTIVE SUMMARY

The FDA approved Depacon® Injection for intravenous (i.v.) use on 12/30/1996. This i.v. formulation is indicated for use in adult and pediatric patients that temporarily cannot use orally administered valproate products. Depacon is indicated as adjunctive and monotherapy in the treatment of epilepsy. The currently approved dosage regimen is a 60-min infusion (≤ 20 mg/min), with an initial dose of 10-15 mg/kg/day. The maximum daily dose is 60 mg/kg.

This supplemental NDA concerns a labeling modification for Depacon to [ ]. The maximum daily dose is unchanged (60 mg/kg). The sponsor states that the major benefit of Depacon infused at higher rates is to extend adequate seizure prophylaxis in a timely manner in subjects at risk for seizure breakthrough.

The submission contains a safety and tolerability study where short-term (5-15 min) infusions of Depacon were given in rates up to 3.0 mg/kg/min to 112 patients. A population pharmacokinetic (PPK) approach was employed in the analysis of the data. One traditional pharmacokinetic study was submitted in the original NDA, and was reviewed again for support of the [ ].

An audit by the Division of Scientific Investigations showed deficiencies in the bioanalytical method. However, the deficiencies are adequately addressed by the sponsor.

The following questions were evaluated in the review:

- Is there a difference in the pharmacokinetics of valproate after an i.v. infusion at 3.0 mg/kg/min compared to 1.5 mg/kg/min (doses expressed as eq. valproic acid)?
- Are there any significant factors that affect the pharmacokinetics of valproate in epileptic patients after an i.v. infusion?
- Is it appropriate to initiate oral therapy (Depakote delayed release tablets) 1-3 h after stop of an i.v. infusion?

It was shown that

1. Depacon administered at infusion rates of 1.5 and 3.0 mg/kg/min over 10 and 5 minutes gave similar total valproic acid (VPA) plasma profiles, where early differences may not have been captured due to the chosen study design (1st plasma sample 15 min after infusion start). A Phase I study, where corresponding VPA infusion rates were given to healthy subjects, showed that total peak VPA concentrations (at infusion stop) were 26% higher after a 5-min infusion and 6% higher after a 10-min infusion, compared to the currently approved 60-min infusion. Simulations showed transient higher free peak VPA concentrations (51% at the higher and 12% at the lower infusion rate compared to a 60-min infusion).
2. Concomitant treatment with anti-epileptic medications known to induce drug metabolism increased total and free clearance of valproate by 61% and 23%, respectively.
3. Initiation of oral therapy 1-3 h after stop of an i.v. infusion, is only recommended after a single i.v. infusion.

From a pharmacokinetic point of view, this supplemental NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Revisions of the proposed label are recommended.

TABLE OF CONTENTS

BACKGROUND

Valproic acid or the sodium salt, sodium valproate, have been approved in the US since 1978, where pharmaceutical formulations intended for both oral and intravenous use are approved. The approved indications are treatment of epilepsy and mania, and migraine prophylaxis. The suggested mechanism of action relates to increased brain concentrations of GABA.
Depacon Injection (valproate sodium eq. 100 mg/mL valproic acid) was approved on December 30, 1996. The i.v. formulation is indicated for use in adult and pediatric patients that temporarily cannot use orally administered valproate products, and should not be used for more than 14 days. Depacon is indicated as adjunctive and monotherapy in the treatment of epilepsy in patients with different types of seizures. The currently approved dosage regimen is a 60-min infusion (≤ 20 mg/min=0.286 mg/kg/min assuming 70-kg body weight), with an initial dose of 10-15 mg/kg/day. The maximum daily dose is 60 mg/kg. The original Clinical Pharmacology and Biopharmaceutics review of this NDA is dated Dec. 15, 1995 (review) and Aug. 1, 1996 (label).

This NDA efficacy supplement (NDA 20-593/S-006) concerns a labeling modification for Depacon to [ ] The maximum daily dose is not changed. The submission contains a safety and tolerability study where short-term (5-15 min) infusion rates up to 3.0 mg/kg/min Depacon were administered to 112 patients. A population pharmacokinetic (PPK) approach was employed in the analysis of the data. One traditional pharmacokinetic study that evaluated different infusion rates was submitted in the original NDA. The study was reviewed again for support of the currently proposed revisions of infusion rates.

The pharmacokinetics of sodium valproate/valproic acid are described by (PDR June 2000):

- Non-linear protein binding at therapeutic drug levels (fraction unbound, fu=0.1 [10%] at 40 µg/mL, fu=0.185 [18.5%] at 130 µg/mL).
- Less than proportional total plasma concentrations (Cp) with increasing valproate doses due to non-linear plasma protein binding. Linear free Cp observed with increasing doses. (Drug-drug interactions may occur during co-administration due to increased free fractions of aspirin and diazepam, also observed *in vitro* for warfarin and tolbutamide)
- A clearance (CL) of 0.56 L/h/1.73 m², and a volume of distribution (V) of 11 L/1.73 m² resulting in a terminal t½ of about 16 h (1000 mg, 60-min infusion), based on total Cp.
- Extensive metabolism (30-50% by glucuronidation, 40% by mitocondrial β-oxidation, 15-20% by oxidation) with less than 3% of the dose excreted unchanged in the urine. (CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, increase valproate CL, resulting in lower valproate plasma levels. Valproate is a weak inhibitor of some CYPs, epoxide hydrase, and glucuronyl transferase. A reduced CL has been reported for diazepam, ethosuximide, lamotrigine, phenobarbital, phenytoin and zidovudine during combination therapy with valproate.)
- No gender differences observed in the pharmacokinetics of valproate
- Lower intrinsic CL (39%) and increased fu (44%) in elderly compared to young adults
- 50% higher clearance in children <10 years (based on body weight). Neonates (0-2 months) had a markedly reduced CL and increased volume of distribution compared to adults.
- Hepatic impairment reduces unbound CL (cirrhosis 50%, acute hepatitis 16%) and increases the fu of valproate (2-2.6-fold). Valproate is contraindicated in hepatic disease.
- Renal failure ($CL_{creatinine}$ <10 mL/min) reduces unbound CL of valproate by 27%. Hemodialysis reduces valproate Cp by 20%, no dose adjustment is needed in this patient group.
- Equal oral and i.v. daily doses resulted in similar valproate plasma concentrations.
- Therapeutic total plasma concentrations of valproic acid are reported to be 50-100 µg/mL (epilepsy treatment).

1. TRADITIONAL PHARMACOKINETIC ANALYSIS: RAPID INFUSIONS OF VALPROATE SODIUM (DATA FROM THE ORIGINAL NDA)

The sponsor submitted one phase I study in the original application (NDA 20-593, Study F90-182; vol. 1.29-1.30), that evaluated different infusion rates (1000 mg eq. valproic acid given over 5, 10, 30 or 60 min). [redacted]

A second phase I study (original NDA 20-593, Study F90-197; vol. 1.33, resubmitted in S-006, vol 1.3) evaluated the steady state pharmacokinetics after an i.v. loading dose of 1000 mg Depacon infused over 10 min, followed by oral divalproex sodium (Depakote) maintenance doses of 500 mg q8h or 250 mg q6h. The oral divalproex dosage regimens were initiated 1 h or 3 h after infusion stop. Due to the study design, the pharmacokinetics of valproate after the i.v. dose could not be separated from the oral administrations. Therefore, the plasma concentrations at infusion stop (10-min) were used and compared to the corresponding levels observed in Study F90-182. Data regarding the oral therapy initiated 1-3 h after the i.v. infusions was also reviewed.

Efficacy was not evaluated in these phase I-studies. Both Phase I-studies were performed in a homogenous population, comprised of healthy, young adult, male volunteers.

1.1 Study Objectives and Methods

Study F90-182:

The objective of the study was to evaluate the safety and pharmacokinetics of valproate from an i.v. infusion of valproate sodium when administered at four different infusion rates. Since this study has previously been reviewed, only a summary will be provided in the present review.

This was a single-dose, four-period crossover, randomized, placebo controlled study in 23 healthy male volunteers. Sixteen of the 23 subjects received active drug infusions, and seven received placebo treatments. There was a 7-day washout between periods. Twenty subjects (mean 24.5 years, range 18-35 years old) completed all study periods. The subjects received placebo or valproate sodium (1000 mg eq. valproic acid) as an i.v. infusion over 5, 10, 30 or 60 min. The valproate infusions corresponded to infusion rates of about 3.0, 1.5, 0.5 and 0.25 mg/kg/min. After infusion stop, the catheter was flushed with 10 mL saline (5-min infusion), to ensure that the total dose was administered to the subject.

Eleven of the 16 subjects that received active treatment were included in the pharmacokinetic analysis (2 subjects were excluded due to analytical problems). Seven subjects received placebo treatment. Three subjects, who received active drug, discontinued the study prematurely after the second period. These three subjects were discontinued after the 30-min and 60-min infusions (0.5 and 0.25 mg/kg/min). One of the subjects was discontinued due to elevated liver enzymes, one did not return to the clinic, and the third subject had taken carisoprodol due to a back injury and was discontinued by the investigator.

Blood samples for analysis of plasma valproate concentrations were collected before infusion start, at the stop of infusion, and at frequent intervals up to 72 h post-infusion. During the 30-min and 60-min infusions, one and two samples, respectively, were collected during the infusion period. A validated GC method was used for the plasma assay, and only total plasma valproate concentrations were determined.

Study F90-197:
A second phase I study evaluated the safety and pharmacokinetics after an i.v. loading dose of 1000 mg Depacon infused over 10 min, followed by oral divalproex maintenance doses of 500 mg q8h or 250 mg q6h (Depakote delayed-release tablets).

This was a multiple-dose, fasting, parallel group, randomized, study in 45 healthy male volunteers (mean 24.6 years, range 18-40 years old). All subjects received the i.v. loading dose of 1000 mg Depacon infused over 10 min. The subjects were randomized to receive different oral regimens:

1. Regimen A: 500 mg eq. valproic acid every 8 h (1500 mg daily dose), where the oral therapy was initiated 1 h after start of infusion. A total of nine consecutive oral doses were administered.
2. Regimen B: 500 mg eq. valproic acid every 8 h (1500 mg daily dose), where the oral therapy was initiated 3 h after start of infusion. A total of nine consecutive oral doses were administered.
3. Regimen C: 250 mg eq. valproic acid every 6 h (1000 mg daily dose), where the oral therapy was initiated 1 h after start of infusion. A total of 12 consecutive oral doses were administered.

Frequent blood samples were collected during the first two dosing intervals (n=5 after oral dose intake), and prior to each subsequent oral dose intake for the remainder of the study. During first dosing interval plasma samples were also collected at 10 min (infusion stop), 30 min, 1 (and 3 h for regimen C) prior to the first oral dose. Total valproic acid plasma concentrations were determined by a validated GC method. The AUC and C_{max} values were calculated for the first two dosing intervals, and the trough concentrations(C_{min} values) were determined throughout the study.

1.2 Results

1.2.1 Pharmacokinetics after i.v. infusions

The valproate plasma concentration-time curves after the four different infusions are depicted in Figures 1.1-1.2 (Study F90-182).

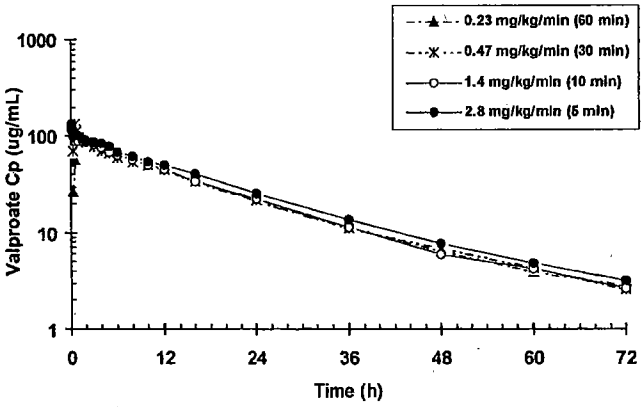


Figure 1.1 Total mean valproate plasma concentration-time curves after 5, 10, 30 or 60-min i.v. infusions of 1000 mg to healthy volunteers (n=11).

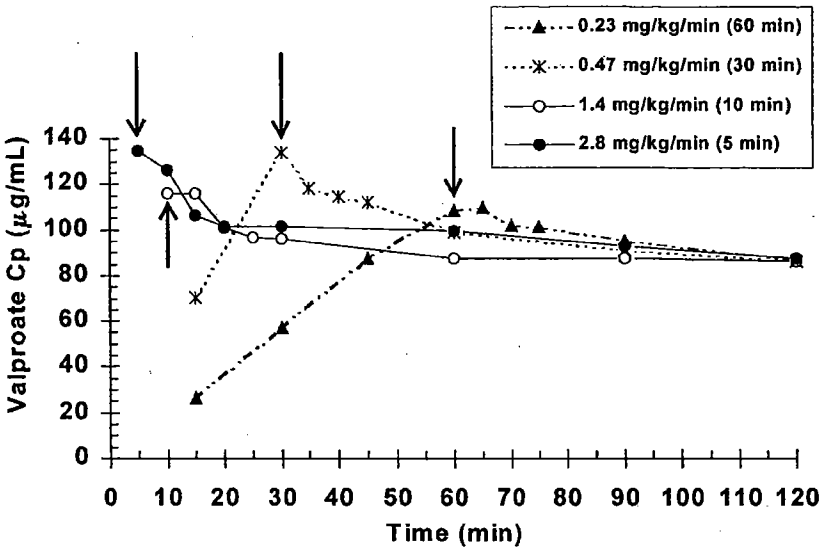


Figure 1.2 Total mean valproate plasma concentration-time curves during the first 2 hours after 5 min (solid line with filled circles), 10 min (solid line with open circles), 30 min (dashed line with star symbol) or 60-min (dashed line with triangles) i.v. infusions of 1000 mg to healthy volunteers (n=11). The arrows indicate stop of infusion.

The pharmacokinetic parameters of valproate were calculated by both non-compartmental and compartmental methods. The results of the non-compartmental analysis are depicted in Table 1.1.

Table 1.1. Mean ± SD pharmacokinetic parameters of valproate following an i.v. infusion of 1000 mg (eq. valproic acid) given over 5, 10, 30 or 60 minutes (Study F90-182, non-compartmental analysis). The means of the actual administered infusion rates are given in the top of the table.

Parameter	60-min infusion 0.23 mg/kg/min (n = 11)	30-min infusion 0.47 mg/kg/min (n = 11)	10-min infusion 1.4 mg/kg/min (n = 11)	5-min infusion 2.8 mg/kg/min (n = 11)
C_{max} (µg/mL)	114.5 ± 7.6	137.0 ± 21.4	122.0 ± 19.7	144.5 ± 31.7
t_{max} (h)	1.08 ± 0.09	0.54 ± 0.08	0.22 ± 0.05	0.20 ± 0.27
$AUC_{(0\text{-}72h)}$ (µg.h/mL)	1546 ± 352	1576 ± 432	1587 ± 405	1798 ± 398
$AUC_{(0\text{-}inf)}$ (µg.h/mL)	1614 ± 393	1645 ± 481	1656 ± 472	1877 ± 447
CL (mL/h)	653 ± 156	649 ± 162	639 ± 145	559 ± 123
Vβ (L)	14.9 ± 4.5	15.1 ± 3.9	14.2 ± 3.8	12.8 ± 3.8
t½β (h)	15.9 ± 2.9	16.3 ± 1.9	15.5 ± 3.1	15.9 ± 2.9

As shown in Table 1.1, the C_{max} of valproate at the end of each infusion was similar, with a trend towards higher concentrations with shortest, 5-min, duration of infusion. Both Vβ and total clearance were 10-15% lower after the 5-min infusion compared to the slower infusion rates. The terminal half-life of valproate was similar between infusion rates, indicating that the differences observed in clearance and volume of distribution for the 5-min infusion compared to the other infusion rates, cancelled out any effects on the overall elimination rate.

The 10-min infusion of valproate sodium (1000 mg eq. valproic acid) corresponds to the slower infusion rate of 1.5 mg/kg/min in the current submission. This infusion rate was also examined in study F90-197. The valproate plasma concentrations at the end of the infusion (10 min) are shown

in Table 1.2, and they are similar to the C_{10min} values observed in study F90-182. The coefficient of variation for C_{10min} was 16-24% in the two studies.

Table 1.2. Mean ± SD (min-max values) of valproate plasma concentrations in 45 healthy male volunteers who received a 10-min i.v. infusion of 1000 mg eq. valproic acid followed by repeated oral doses of divalproex sodium (Study F90-197). The actual administered infusion rates and body weights are included in the table.

Treatment	No. Subjects	Weight (kg)	Inf. Rate (mg/kg/min)	$C_{10\ min}$ at infusion stop (µg/mL)
1000 mg i.v. loading dose (500 mg q8h, 1 h after infusion start*)	15	78.4 ± 10.8 (61.7-101.6)	1.3 ± 0.16 (0.98-1.6)	106 ± 31 (67-167)
1000 mg i.v. loading dose (500 mg q8h, 3 h after infusion start*)	15	76.6 ± 7.7 (61.0-85.7)	1.3 ± 0.14 (1.2-1.6)	113 ± 38 (6-168)
1000 mg i.v. loading dose (250 mg q6h, 1 h after infusion start*)	15	78.5 ± 11.5 (61.2-103.4)	1.3 ± 0.18 (0.97-1.6)	95 ± 23 (59-154)

*1st oral dose intake 1 or 3 h after start of infusion

1.2.2 Pharmacokinetics after oral administration with an i.v. loading dose

The pharmacokinetics of valproic acid after repeated oral doses were determined after the two first dosing intervals in healthy male volunteers who received a 10-min loading i.v. infusion of 1000 mg eq. valproic acid prior to repeated oral doses of valproex sodium (500 mg q8h: 1st dose 1 or 3 h after start of infusion, or 250 mg q6h: 1st dose 1 h after start of infusion). The results are shown in Table 1.3.

Table 1.3 Pharmacokinetics (mean±SD) of valproic acid in healthy male volunteers (n=15 per regimen) after the first and second oral dose intake. A 10-min i.v. loading infusion of 1000 mg eq valproic acid preceded the oral doses with 1 or 3 h.

Parameter	Regimen A: 500 mg q8h, 1 h after infusion-start		B: 500 mg q8h, 3 h after infusion-start		C: 250 mg q6h, 1 h after infusion-start	
	Oral 1*	Oral 2**	Oral 1*	Oral 2**	Oral 1*	Oral 2**
AUC (µg.h/mL)	642 ± 104	616 ± 108	530 ± 92	447 ± 107	473 ± 71	357 ± 63
C_{max} (µg/mL)	105 ± 17	68 ± 17	81 ± 13	71 ± 16	100 ± 21	69 ± 11
C_{min} (µg/mL)	61 ± 15	40 ± 10	54 ± 10	44 ± 12	63 ± 9	51 ± 10

*1st dose for Regimens A, B, C: AUC 1-9 h, 3-11 h, and 1-7 h, respectively. ** 2nd dose for Regimens A, B, C: AUC 9-17 h, 11-19 h, and 7-13 h, respectively

The contribution of the intravenous dose to the oral AUC values was more substantial after the first than the second dose (statistically significant within each regimen, $p<0.01$). The AUC was also higher after the first two doses, when the oral dosage regimen of 500 mg q8h was initiated 1 h compared to 3 h after start of infusion. However, the trough levels prior to the subsequent oral doses (starting on Dose 4 or 5) were comparable between the dosage regimens, as shown in Figure 1.3. The lower C_{min} values after the 250 mg q6h regimen (Doses 5-9), is consistent with the lower total daily dose (1000 mg *vs.* 1500 mg for the other regimens).

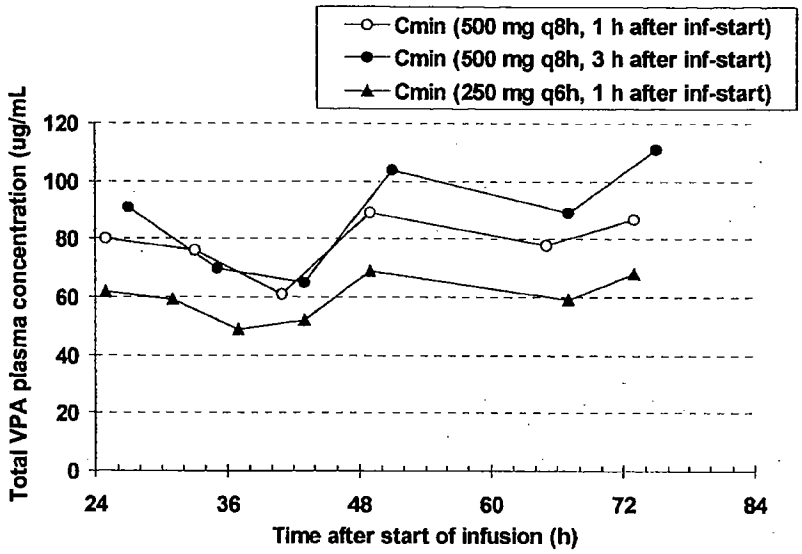


Figure 1.3. Total trough (average C_{min}) plasma concentrations after repeated oral doses of 500 mg eq valproic acid q8h (Dose 4-9), or 250 mg q6h (Dose 5-12) to healthy, male subjects (n=15/group). The first oral dose was given 1 or 3 h after an i.v. loading dose.

There was a trend of higher C_{min} values during the 3rd day (<15%) of oral dosing compared to the 2nd day. However, steady state plasma concentrations with trough concentrations about 50 µg/mL or higher, appeared to be achieved within 24 h after the initial i.v. loading dose.

1.2.3 Safety

In study F90-182 vital signs (heart rate, systolic and diastolic blood pressure) were closely monitored. According to the sponsor, there were no statistically significant differences in the vital signs, small average decreases in blood pressure (<4 mm Hg) and heart rate (<2 bpm) were observed. Three subjects had elevated SGOT/SGPT values. Three subjects (23%) who received the 5-min and 10-min infusions reported injection site pain, dizziness and taste perversion. The subjects who received valproate at slower infusion rates or the subjects who received placebo infusions did not report these adverse events.

In Study F90-197, 11 subjects reported 21 adverse events during the study. The most frequent adverse events were abdominal pain, headache, pain or reaction at injection site, diarrhea, nausea and vomiting.

1.3 Comments

It has been shown that increasing valproate doses yield less than proportional total plasma concentrations (Cp) due to non-linear plasma protein binding, but free Cp increase linearly with increasing doses. However, in study F90-182, the pharmacokinetic parameter estimates were only calculated from total valproate plasma data, as free concentrations were not determined. Although the total dose remained constant in the study, the C_{max} of valproate at the end of each infusion would be expected to be higher after the higher infusion rates. As would be expected for a low extraction drug where the unbound fraction of drug in plasma increases, a decrease in $V\beta$ was observed. However, instead of a corresponding expected increase in CL, a small decrease in CL was observed, which may indicate saturation of one metabolic pathway. According to the

sponsor, saturation of the β-oxidation pathway has been demonstrated at Cps close to 100 μg/mL. The terminal t½ was around 16 h after all four dosing regimens. No firm conclusions regarding changes in CL or Vβ can be made, since unbound valproate plasma concentrations were not determined.

Acceptable steady state trough plasma levels were reached within 24 h after repeated oral doses of valproex sodium (Depakote delayed-release tablets, q6h or q8h) that were preceded by an intravenous loading dose of 1000 mg eq. valproic acid (actual infusion rate of 1.3 mg/kg/min over 10 min). There intravenous loading dose gave higher oral C_{max} and AUC values (about 20% on average) after the first two doses when the oral therapy (500 mg q8h) was initiated 1 h compared to 3 h after the intravenous dose. However, the intravenous loading dose seemed reasonably well matched to the oral regimens.

2. POPULATION PHARMACOKINETIC ANALYSIS: RAPID INFUSIONS OF VALPROATE SODIUM

2.1 Study Objective and Methods

The sponsor has submitted one phase IIIB study in NDA 20-593/S-006. The study is entitled 'The safety and tolerance of intravenous Depacon at an infusion rate up to 3.0 mg/kg/min in subjects with epilepsy' (Study M98-938; population pharmacokinetic data: NDA volume 1.2; clinical data: NDA volumes 1.3-1.24). Efficacy was not evaluated in this study.

The population pharmacokinetic data was reviewed by Dr. Elena V. Mishina, pharmacometrics specialist ([ ] analysis), and Donald J. Schuirmann, expert mathematical statistician (SAS analysis of covariates). The main conclusions of the [ ] and SAS analyses are incorporated into the present review, for details, please refer to Appendix 1.

The primary study objective was:

- To evaluate safety of rapid infusions (1.5 and 3 mg/kg/min) of a total dose of 15 mg/kg of valproate sodium to an epileptic population. Adverse events, clinical laboratory data and blood pressure recordings were evaluated for safety.

The secondary study objective was:

- To evaluate the relationship between valproate administration and adverse events observed with the new dosing strategy.

This was an open-label, prospective, multi-center, randomized, parallel group study in 112 patients with epilepsy. The study consisted of two phases, an infusion phase and an optional maintenance phase. During the infusion phase, up to four infusions were allowed within 24 hours (total maximum dose per infusion was 15 mg/kg), with at least 2 hours separating each infusion. Once a target valproate plasma concentration (Cp) of 50-100 μg/mL was attained, or the investigator assessed the concentration to be adequate, the subject could have been given oral valproate for use outside the protocol or continued on Depacon for up to 14 days during the maintenance phase.

The eligibility of the subjects for study participation was assessed via medical and seizure histories, abbreviated physical exam with vital signs, laboratory tests (hematology, chemistry, and plasma valproic level determinations), and brief neurological and cardiologic examinations. A baseline electrocardiogram (ECG) was also to be performed. The main inclusion criteria were complex partial or absence seizure types (no seizures 24 h prior to infusion), pre-infusion valproate Cp <50 μg/mL, male and female patients older than 2 years of age, no history of cardiac rhythm disturbances, orthostatic hypotension or syncope.

The patients were randomized in a 2:1 ratio at each center to receive either 3.0 or 1.5 mg/kg/min valproate infusions, with a total dose of up to 15 mg/kg per infusion (5 or 10 min duration of infusion). The patients were monitored for any adverse events during and after the infusion. If a clinically significant change in blood pressure (BP) with symptoms occurred at any time during the study, the patients were discontinued. Multiple BP measurements (pre-infusion, and 5, 10, 20 and 30 min post-infusion during the infusion phase, as well as pre-infusion and 5 minutes post-infusion during the maintenance phase) were recorded as part of the overall safety assessment. A continuous ECG evaluation was performed for the duration of each infusion and for 5 min post-infusion during the infusion phase. If any abnormal rhythm changes were noted, the rhythm evaluation was continued until the changes resolved. If the change in the ECG was considered to be clinically significant and led to a discontinuation from the study, it was reported as an adverse event.

Blood samples for analysis of total and free valproate plasma concentrations were to be collected pre-infusion (0), 5 min after infusion stop, 30 min after infusion stop (optional sample), 1, 2, 3, 4, 5 and 6 h after stop of infusion. The result from the 1-h post-infusion measurement of each infusion was to be used to determine a patient's need for a subsequent infusion and the dose of that infusion (max. 15 mg/kg). In most situations, the first infusion was to be followed by a maintenance regimen of oral or i.v. valproate. However, if after the first infusion, plasma levels were below the target range (50-100 μg/mL), up to 3 subsequent infusions (max. 15 mg/kg) each could be administered at the randomized rate within 24 h. A minimum of a 2-hour time lapse was to occur between each infusion.

2.2 Population pharmacokinetic analysis

2.2.1 Objectives

The objectives of the data analyses were to:

1. Compare valproic acid (VPA) pharmacokinetics in subjects receiving Depacon at the rates of 1.5 *vs.* 3.0 mg/kg/min, and in metabolically induced *vs.* non-induced patients. Metabolic induced status was assumed if the patient was taking phenytoin, carbamazepine, and/or phenobarbital.
2. Determine predictors of C_{max} and clearance as a function of demographics and dosing rate
3. Identify significant factors affecting the binding of VPA to albumin
4. Assess the accuracy of dosing and re-dosing strategy employed using the subject's weight and an assumed population volume of distribution (V_{pop})
5. Evaluate the association of the adverse events with VPA plasma concentrations

2.2.2 Pharmacokinetic Analyses

The bioanalytical method and results are described in section 2.3.2.

Non-compartmental analysis

The sponsor tabulated the observed C_{max} for total and free VPA, calculated the area under the plasma concentration-time curve up to the last plasma sample (AUCt), and presented the summary statistics for all patients included in the non-parametric analysis.

Population pharmacokinetic analysis

One-compartment and 2-compartment models were evaluated for the most appropriate description of the pharmacokinetics of free and total VPA, with and without the incorporation of the induction status. The random residual error model for both total and free VPA population models was assumed to be the sum of additive and proportional models.

$Cp = F \cdot (1 + \varepsilon_1) + \varepsilon_2$; where ε_1 and ε_2 are the proportional and additive error terms

Covariate analysis

The Sponsor chose to perform covariate analyses using SAS. For the responses log(C_{max}) (observed C_{max} from individual concentration-time profiles) and log(CL) (CL = clearance, post hoc estimates obtained from [ ]), for both free valproic acid (VPA) and total VPA, where multiple regression models in which certain potential covariates – induction status, weight, age, albumin, gender, presence of lamotrigine, creatinine, and dosing rate - were examined as potential explanatory variables for the responses. Similarly for the response K1 (protein binding constant, post hoc estimates from [ ] runs) induction status, cholesterol, creatinine, and age were considered as potential explanatory covariates. The sponsor's covariate analyses examined the linear relationship between the response and the selected covariates. The Sponsor used the Forward Selection method. In this method, covariates are added to the model one at a time, based on which covariate provides the most statistically significant improvement to the fit of the model. Once the first covariate is chosen, other covariates are considered for inclusion in the model based on the improvement of fit they produce in a model that includes the first covariate selected. Covariates are sequentially added to the model in this fashion until none of the remaining covariates give a statistically significant improvement to the fit of the model (the sponsor chose a level of significance of 0.10). The sponsor forced one covariate, induction status, to be in all of the regression models, regardless of statistical significance. This was done for physiologic reasons.

2.3 Results

2.3.1. Demographics and study conduct

Twelve centers in the U.S. enrolled patients into the study. One hundred twelve (112) patients were randomized and received study drug. Ten percent of the participating patients (n=12) were less than 18 years old. The demographics of the randomized patients are depicted in Table 2.1.

Table 2.1. Demographics of the 112 patients who received valproate sodium (Depacon as a 1.5 mg/kg/min (n=40) or 3.0 mg/kg/min (n=72).

Demographic Characteristic	Depacon® Treatment Group n (%) 1.5 mg/kg/minute (N = 40)		3.0 mg/kg/minute (N = 72)		P-value
Sex					
Female	18	(45%)	33	(46%)	>0.999
Male	22	(55%)	39	(54%)	
Race					
Caucasian	28	(70%)	50	(69%)	0.348
African-American	10	(25%)	11	(15%)	
Asian/Pacific Islander	0	(0%)	2	(3%)	
Other	2	(5%)	9	(13%)	
Age (years)					0.474
Mean (SD)	37.7 (15.49)		35.5 (15.84)		
Min - Max	7.0 - 77.0		1.0 - 79.0		
Weight (kilograms)					0.116
Mean (SD)	81.6 (26.11)		73.8 (24.14)		
Min - Max	28.0 - 155.5		8.6 - 145.2		
Height (centimeters)	(N = 37)		(N = 63)		0.443
Mean (SD)	168.0 (13.90)		165.2 (19.52)		
Min - Max	125.0 - 198.1		72.5 - 193.0		

Cross-reference: Table 14.1__2.1

The demographics were similar between the patients receiving the two different infusion regimens. Concomitant anti-epileptic medications were allowed in the study, and the patients received other anti-epileptic drugs concomitantly. The patients were classified as having non-

induced or induced status based on the medical history of concomitant drug intake of anti epileptic drugs known to induce metabolic clearance. A patient was considered to be induced if he or she had been dosed with an inducer on the study day or within 7 days prior to the study drug infusion. A binary classification (induced=1, noninduced=0) was used for the induction status of each patient. The concomitant anti-epileptic medications used by the patients in the study are listed in Table 2.2.

Table 2.2. Co-administered anti-epileptic medication in patients (Study M98-938).

	Number (%) of subjects		
Anti-epileptic	**1.5 mg/kg/min (n=40)**	**3.0 mg/kg/min (n=72)**	**Total (n=112)**
Carbamazepine*	**11 (27.5%)**	**14 (19.4%)**	**25 (22.3%)**
Lamotrigine	**7 (17.5%)**	**15 (20.8%)**	**22 (19.6%)**
Phenytoin*	**10 (25.0%)**	**12 (16.7%)**	**22 (19.6%)**
Tiagabine	**2 (5.0%)**	**1 (1.4%)**	**3 (2.7%)**
Phenobarbital*	**3 (7.5%)**	**5 (6.9%)**	**8 (7.1%)**
Primidone	**2 (5.0%)**	**0**	**2 (1.8%)**
Lorazepam	**3 (7.5%)**	**6 (8.3%)**	**9 (8.0%)**
Gabapentin	**5 (12.5%)**	**11 (15.3%)**	**16 (14.3%)**
Topiramate	**4 (10.0%)**	**6 (8.3%)**	**10 (8.9%)**

*Inducer of valproate metabolism (lower valproate Cp's have been reported during concomitant therapy)

The majority of randomized patients received only one infusion of valproate sodium. Two patients randomized to receive 3.0 mg/kg/min also received a second infusion during the first day. One additional patient (3.0 mg/kg/min group) received two i.v. infusions during the maintenance phase. The administered infusion rates of valproate sodium are shown in Table 2.3.

Table 2.3. Distribution of actual infusion rates of valproate sodium used in the study.

Randomized Depacon® Treatment Group			
1.5 mg/kg/minute (N=37)		3.0 mg/kg/minute (N=75)	
Rate Received	Number of Subjects	Rate Received	Number of Subjects
1.0 - 1.1	2	>1.4 - 1.5	1
>1.3 - 1.4	1	>1.9 - 2.0	2
>1.4 - 1.5	26	>2.0 - 2.1	1
>1.5 - 1.6	1	>2.1 - 2.25	2
>1.6 - 1.7	2	>2.3 - 2.4	1
>1.8 - 1.9	1	>2.4 - 2.5	2
>1.9 - 2.0	1	>2.5 - 2.6	2
>2.4 - 2.5	1	>2.8 - 2.9	1
>2.9 - 3.0	2	>2.9 - 3.0	52
		>3.0 - 3.1	6
		>3.2 - 3.3	2
		>3.3 - 3.4	1
		>3.6 - 3.7	1
		>3.7 - 3.8	1

Cross-reference: Appendix 16.2__5.1

Three subjects randomized to receive 1.5 mg/kg/min and 6 subjects randomized to receive 3.0 mg/kg/min actually received drug at an infusion rate closer to the opposite treatment group during the infusion phase. The average dose given was 14.6 mg/kg, or approximately 1100 mg. Although the total dose was the same for both groups, the actual mean dose per infusion was 9.8% higher in the slower infusion rate group (1240 mg; n=28), compared to the higher infusion rate group (1133 mg; n=54).

2.3.2. Bioanalytical methods

The 'on-the-spot' checks of total valproic acid (VPA) plasma concentrations at each center were performed at certified local laboratories.

[redacted] performed the analyses of total and free VPA plasma concentrations for the pharmacokinetic evaluation. A total of 791 free VPA and 821 total VPA results were reported. The TDx/TDxFLx Valproic Acid assay and Free Valproic assay used, are reagent systems for quantitative measurements of total and unbound VPA in plasma (or serum). The assays utilize fluorescence polarization immunoassay (FPIA) technology.

The assays had a limit of quantitation for total and free VPA in plasma of 12.5 and 2 µg/mL, respectively. The assays were calibrated in the range of 12.5-150 µg/mL for total valproic acid, and in the range of 2.0-25.0 µg/mL for free valproic acid. Three quality controls (QCs), low, medium and high concentrations, were included in each analytical sample run (20 samples per run). The intra-assay precision had a coefficient of variation (CV) <5% at all QC levels, and the % recovery was 97-106%. The inter-assay precision had a coefficient of variation (CV) <8% at all QC levels, and the % recovery was 100-109%. The assay precision and accuracy is satisfactory. During the study analysis the QC's should be within 10% of the nominal value, or the assay was to be repeated. All analyses were acceptable, except one run where two out of three QCs was deemed acceptable. However, the sponsor deemed this analytic run acceptable.

All samples were analyzed within 2 weeks of shipment from the investigational sites or the sponsor. The Division of Scientific Investigations (DSI) audited the analytical facility. It was found that the long-term stability of the plasma samples used for determination of free valproic acid concentrations has not been demonstrated. The sponsor was contacted to provide additional information, see Section 3 (Audit by the Division of Scientific Investigations). After review of the sponsor's response, the analysis of free valproic acid concentrations was deemed acceptable (see Section 3).

For the pharmacokinetic analyses some data was censored from the data sets. All plasma concentration data from patients with a total VPA pre-dose concentration ≥50 µg/mL, and additionally, a few data points which were considered as inconsistent, were not included in the pharmacokinetic analyses. The additional, censored data represented <3% of the total number of samples.

2.3.3. Non-compartmental analysis

Ninety-six (96) patients were included in the non-parametric analysis. The 96 patients received a total dose of 15 mg/kg and had no positive pre-dose valproic acid (VPA) plasma concentrations. From this group, 54 patients received the dose as a 5-min infusion and 28 patients as a 10-min infusion. Fifty-two (52) patients had induced status, and 44 were considered as not induced. Data was available for 13 additional patients, who had positive pre-dose VPA plasma concentrations or did not receive a total dose of 15 mg/kg, but was not included in this analysis.

The sponsor compared the C_{max} and $AUC_{0-6\,h}$ (AUCt) values for two infusion groups. Because the concentration at the end of infusion was measured only in 2 patients, and on average plasma samples were taken about 12 min after the 5-min infusion, and 5.6 minutes after the 10-min infusion, the comparison of C_{max} values cannot be performed in this setting. The $AUC_{0-6\,h}$ values calculated for total and free VPA were somewhat dissimilar between both infusion rates and non-induced status, but the difference was <20%. The results for C_{max} and $AUC_{0-6\,h}$ separated into infusion rates or induced/non induced status, are depicted in Table 2.4.

Table 2.4. Non-compartmental analysis of C_{max} and $AUC_{0\text{-}6\ h}$ (Total and free VPA concentrations). Note that the observed C_{max} value is collected 12 min after infusion stop of the 3.0 mg/kg/min (5-min) infusion, and 5.6 min after infusion stop of the 1.5 mg/kg/min (10-min) infusion.

Category	n	Total VPA concentrations C_{max} (µg/mL)	Total VPA concentrations $AUC_{0\text{-}6h}$ (µg.h/mL)	Free VPA concentrations C_{max} (µg/mL)	Free VPA concentrations $AUC_{0\text{-}6h}$ (µg.h/mL)
R_{inf} 1.5 mg/kg/min	**28**	**96.9 ± 17.9**	**370 ± 92.4**	**16.3 ± 7.78**	**45.8 ± 23.5**
R_{inf} 3.0 mg/kg/min	**54**	**92.9 ± 19.0**	**359 ± 83.6**	**13.8 ± 7.34**	**37.5 ± 17.2**
Non-induced patients*†	**44**	**96.4 ± 18.3**	**392 ± 74.9**	**14.1 ± 7.64**	**42.3 ± 18.0**
Induced patients*†	**52**	**92.6 ± 17.6**	**329 ± 83.0**	**14.7 ± 6.89**	**38.7 ± 20.7**
All patients †	**96**	**94.3 ± 17.9**	**359 ± 84.8**	**14.4 ± 7.20**	**40.4 ± 19.4**

*Concomitant medications of anti-epileptic medications reported to be non-inducing or inducing metabolic CL of VPA; † All patients who received a 15 mg/kg dose, irrespective of infusion rate.

Due to the study design, no information is available on the VPA concentrations at the end of the infusion, 5 and 10 min, respectively. Since the C_{max} values presented in Table 2.4 depicts VPA plasma concentrations approximately 15 min after start of infusion irrespective of rate and duration, these samples are of limited value for a comparison of the two infusion rates during the period of anticipated maximal plasma concentrations in each patient. However, the $AUC_{0\text{-}6\ h}$ values are somewhat less sensitive, and could serve as a comparison between the two infusion rates. There was an 18% decrease in free, but no change in total $AUC_{0\text{-}6\ h}$ after the 3.0 mg/kg/min compared to the 1.5 mg/kg/min infusion, that may point to a higher unbound CL after the more rapid infusion. There was also a trend of lower $AUC_{0\text{-}6\ h}$ values in induced patients (free VPA: -10%; total VPA –16%), compared to the non-induced patients, irrespective of infusion rate. Both induction status and rate of infusion may influence the pharmacokinetics of VPA according to the non-compartmental analysis, the influence of the induction status was not separated out in the two groups with different infusion rates.

2.3.4. Population pharmacokinetic analysis

A total of 1498 valproic acid (VPA) plasma concentrations from 109 subjects were used for [ ] analyses. The only covariate assessed by [ ] was the influence of the induction status on clearance (CL) of total and free VPA. The influence of all other covariates: age, weight, albumin, gender, lamotrigine, creatinine and dosing rate on C_{max}, CL, and the protein binding constant K1 for both total and free drug were explored by the sponsor using the SAS analyses of variance.

The sponsor selected a 1-compartmental model for total VPA and a 2-compartmental model for free VPA. The sponsor justified the choice of these models on estimations of clearance values, which are close to those described in the literature. Due to the short sampling period of 6 h (VPA has a terminal t½ of 16 h), the CL was overestimated, and the determined values can only be used in comparison to each other, no cross-study comparisons would be reliable. The FDA's assessment of the models of free and total VPA indicates that both models have a room for improvement, especially for the free drug (see Appendix 1 for further discussion). The improvement of fit in [ ] usually is achieved by incorporation of the covariates into the model(s), however, a different approach (SAS analysis), was chosen to evaluate the covariates by the sponsor. The SAS procedure is an acceptable method of analysis.

The population pharmacokinetic estimates for total and free valproate are listed in Table 2.5.

Table 2.5. Central population estimates of clearance (CL) and apparent volume of distribution (V) for total valproate (1-compartment model) and free valproate (2-compartment model).

	Total valproate		Free valproate	
Parameter	**Description**	**Estimate ± SE**	**Description**	**Estimate ± SE**
θ_1	CL (L/h)	1.21 ± 0.0854	CL (L/h)	18.4 ± 8.17
θ_2	V (L)	12.3 ± 0.373	V_1 (L)	2.09 ± 2.43
θ_3	IND* (L/h)	0.739 ± 0.241	Q (L/h)	63.7 ± 61.7
θ_4			V_2 (L)	65.8 ± 25.7
θ_5			IND* (L/h)	4.30 ± 2.73
η_1		0.205 ± 0.0530		0.560 ± 0.560
η_2		0.168 ± 0.117		0.0372 ± 0.0460

θ = Population parameter; η = inter-subject variability; *Indicator variable for induction status where IND = increase in CL due to induction; Q = Inter-compartmental clearance; V_1=Initial volume of distribution; V_2=Volume of distribution during the terminal phase

The estimated effect of co-administered anti-epileptic drugs known to be inducers was a 61% increase in total clearance, and a 23% increase in free clearance of valproate. Due to the limited period of blood sampling (6 h) the clearance values were overestimated, compared to previous determinations. The estimated terminal half-life for total valproate was about 7 h ($t_{½}$=ln 2*V/CL; Table 2.5), which is shorter than the previously reported $t_{½}$ of 16 h.

The observed total and free plasma concentrations were fit to a second order polynomial equation [ ], as shown in Figure 2.1.

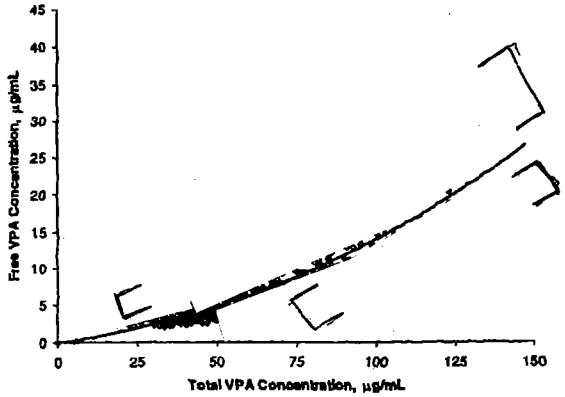


Figure 2.1. Observed free *vs.* total VPA plasma concentration profile. The solid line indicates the fit to a second order polynomial equation (C_{free} = 0.0009*C_{total}^2 + 0.0527 *C_{total}; r^2=0.6718).

As shown in Figure 2.1, there is a non-linear increase in free VPA concentrations in the therapeutic plasma concentration range of 50-150 µg/mL. For all free and total concentration pairs in the 1.5 mg/kg/min group the median free fraction was 0.11 (range [ ]; n=169), and in the 3.0 mg/kg/min group the median free fraction was 0.095 (range [ ]; n=362). However, since the true C_{max} was not captured at the infusion stop, the two infusion rates may differ during and immediately after the stop of infusion, which was not captured due to the sampling schedule used in the study.

In addition, as previously stated, the long-term stability of the frozen samples for determination of free valproic acid concentrations has not been demonstrated. This makes the free valproic acid concentration data from this study questionable. The sponsor was therefore requested to provide simulations of free plasma concentrations obtained after different infusion rates developed from data from a Phase I study (Study F90-182), the simulations are reported in Section 3.2.

2.3.5. Covariate analysis

In the covariate analysis, the sponsor forced one covariate, induction status, to be in all of the regression models, regardless of statistical significance. This was done for physiologic reasons. The additional covariates selected by the sponsor had to reach a level of significance of 0.10, to be deemed to influence the pharmacokinetics of valproic acid (VPA).

The covariates selected were:

ln(C_{max}) total VPA	induction status, weight, albumin, dosing rate
ln(C_{max}) free VPA	induction status, weight, age, dosing rate
ln(CL) total VPA	induction status, weight
ln(CL) free VPA	induction status, weight, age, dosing rate
K1	induction status, age

In summary, the rate of infusion (dosing rate) of valproate influenced free VPA C_{max} and unbound clearance (CL). The free clearance of VPA was higher at the 3.0 mg/kg/min infusion rate ($p=0.0665$), increasing weight, induction status and a younger age ($p=0.0738$). According to the sponsor's main report, infusion rate and age were not significant co-factors for free VPA CL, however, according to the statistical report, these factors influenced the free VPA CL ($p<0.10$). An examination of the post-hoc free VPA CL values (prior to covariate analysis) showed that the difference was indeed nominal (3.0 mg/kg/min: free CL 19.4±10.1 L/h; 1.5 mg/kg/min: free CL 18.0±8.2 L/h). Induction status and weight influenced the total clearance of VPA.

On the other hand, the true C_{max} was not captured at the infusion-stop due to the scheduled sampling times. The C_{max} after the 3.0 mg/kg/min infusion rate was predicted to be about 10% higher than after the 1.5 mg/kg/min infusion rate. However, due to the sampling schedule, there was a significant difference in the total C_{max}, where the higher infusion rate was associated with a lower C_{max}.

The protein binding constant (K1) was marginally influenced by induction status ($p=0.0536$) and age ($p=0.0817$). Cholesterol and creatinine levels were not found to influence protein binding.

2.3.6. Adverse events and changes in blood pressure

The relationship between adverse events and valproic acid (VPA) plasma concentrations was compared for the two groups receiving infusions of 1.5 and 3.0 mg/kg/min. Only adverse events during first 6 hours after the infusion were evaluated. The incidence of adverse events was low, and no formal statistical analysis was performed. The majority of the adverse events were observed during the infusion in the initial phase of the study.

FDA plotted diastolic and systolic blood pressures *vs.* free and total VPA plasma concentrations and analyzed the plots (see Appendix 1 for figures). A shallow slope for the difference in the plot of diastolic blood pressure (DBP) *vs.* free VPA plasma concentrations was observed. All other plots showed equal distribution of the data around the zero lines, indicating that no other apparent relationships between blood pressure and free and total VPA plasma concentrations were observed.

2.3.7. Dosing and re-dosing strategies

One of the objectives in the study was to assess the accuracy of the dosing and re-dosing strategy using the following equation:

$$D = W \times \Delta Cp \times V_{est}$$

where D = dose (mg), W = body mass (kg), ΔCp = desired increase in plasma valproate concentration (mg/L) and V_{est} = estimated apparent volume of distribution (0.2 L/kg).

Since almost no patients received a second dose, the re-dosing strategy was not evaluated during the study. Six patients with measurable VPA concentrations before start of infusion were evaluated prospectively, and the data from all patients were evaluated retrospectively by use of the equation above. The C_{max} was underestimated by 22% or less. However, because the true C_{max} at the end of the infusion was not captured, the underestimation is likely to be of greater magnitude. The sponsor hypothesizes that the underestimation is due to the use of the V_{est} of 0.2 L/kg, derived from the volume of distribution at steady state determined in earlier studies, and that the initial volume of distribution would give a better prediction. In spite of this, the use of the equation in its current form is not a good predictor of dose calculations since it leads to under estimations of plasma VPA concentrations at the stop of infusion.

The sponsor used the population pharmacokinetic estimates determined in the study to simulate plasma VPA profiles of oral divalproex substitution therapy (Depakote delayed release tablets, 500 mg q8h) started at 1 or 3 h after end of infusion (10-min infusion, 1000 mg Depacon). The simulations are not deemed useful, since the calculated pharmacokinetic parameters do not reflect the true parameters, due to the study design. The simulated plasma VPA concentrations are likely to be under-estimated due to the high clearance value (1.21 L/h), and possibly the volume of distribution value (12.3 L which approximates 0.18 L/kg based on a body weight of 70 kg) used in the simulations.

2.4 Comments

The following conclusions can be made for the population pharmacokinetic analysis:

1. Due to the study design, it is difficult to compare the two infusion rates (15 mg/kg as a 5-min or 10 min infusion) during the time period where differences are most likely to occur, e.g. during the infusion and immediately after infusion stop. The first plasma samples were collected 15 min after start of infusion, and sampling continued up to 6 h after the infusion. Therefore, potential differences in C_{max} may not have been captured, that may be important due to the non-linear valproate plasma protein binding. Although the total and free valproate plasma levels were comparable between infusion rates 15 min post-infusion, more information about potential differences would have been beneficial, to assess the influence of potential transient, high free drug concentrations on the pharmacokinetics of valproate during or at least, at the stop of infusion. Due to rapid distribution of valproate, potential differences in the initial total and free drug concentrations between the two infusion rates may not have been captured.
2. Total clearance was estimated to be increased by 61% in patients that were metabolically induced, a corresponding increase of 23% in free clearance of valproate was determined. Metabolic induced status was assumed if the patient also was taking phenytoin, carbamazepine, and/or phenobarbital.
3. The higher infusion rate (3.0 *vs.* 1.5 mg/kg/min eq. valproic acid) was associated with a somewhat higher free clearance of valproate compared to the slower rate of infusion (p=0.0665). Infusion rate also influenced total and free C_{max}, but due to the reasons discussed in comment 1, these changes are difficult to interpret. Other factors that were found to influence the pharmacokinetic parameters of valproate were weight and age, which has been

described earlier in the original NDA. However, the sponsor notes that weight, age and gender were somewhat confounded, with children and females having lower weights.

4. The dosing and re-dosing strategy employed is deemed to be less useful, since the study design led to imprecise estimates of pharmacokinetic parameters compared to earlier data.
5. No relationship was observed between adverse events and VPA plasma concentrations. No analysis was performed due to the low incidence of adverse events. No (or weak) relationships were observed between blood pressure and VPA plasma concentrations.
6. The population pharmacokinetic model development could be enhanced. The FDA diagnostic plots for free and total VPA indicate that both models have a room for the improvement, especially for the free drug. The improvement of fit in [ ] usually is achieved by incorporation of the covariates into the model(s). Only induction status was incorporated into the [ ] models. Instead, the sponsor chose to evaluate the influence of covariates by a SAS analysis (see comment 7). The model development for protein binding showed a marginal difference between the models with one and two binding sites. The chosen model (a second order polynomial equation) does not have any physiologic meaning, but describes the relationship between free and total valproate concentrations.
7. The Sponsor's covariate analyses only considered linear relationships between covariates and response. This is not uncommon in exploratory analyses, since even nonlinear relationships might be expected to have a linear component. The topic whether nonlinear models should have been considered for one or more of the candidate covariates was not addressed in this review. Given that only linear relationships were considered, the use of SAS procedures, such as SAS PROC GLM and SAS PROC REG, is appropriate.

3. AUDIT BY THE DIVISION OF SCIENTIFIC INVESTIGATIONS

3.1 DSI Audit

The Division of Scientific Investigations (DSI) audited the analytical facility [ ] [ ] that analyzed samples from the PPK study (M98-938). It was found that the long-term stability of the plasma samples has not been demonstrated. According to the method description, frozen plasma samples should not be stored longer than two weeks prior to analysis of free VPA concentrations. The method description does not state a maximum time limit of storage for analysis of total VPA plasma concentrations. By comparing investigational dates and dates of plasma analysis, it was found that only 30% (approximately) of the samples for determination of free VPA plasma concentrations were likely to have been analyzed within 2 weeks of collection. The estimated storage times prior to analysis for all other samples ranged from 3 weeks up to 24 weeks. The sponsor was contacted, and asked to provide any documentation supporting the longer storage periods for the plasma samples, and also provide simulations of free plasma concentrations from a Phase I study.

The sponsor could only supply information regarding long-term stability data for total valproic acid concentrations in frozen samples. Long-term stability of frozen samples has been demonstrated for up to 4.7 years by two independent laboratories. The sponsor also provided information on the chemical stability of valproic acid, which is excellent. The concern, is not the stability of the analyte, but the potential changes over time in the fraction of free (unbound) drug relative to total concentrations in frozen plasma samples. The analytical facility has started long-term stability testing of frozen samples for analysis of free valproic acid concentrations, but data is not yet available. The analytical facility has generated data on the stability in sample aliquots that were thawed (after 48 h at –20°C) and stored in room temperature for 24 and 48 h, respectively. It was determined that the free valproic acid concentrations were virtually unchanged for this time period.

During the DSI audit it was also noted that a few samples (both total and free concentrations of VPA; max 40 samples out of a total of 1498) should not have been included, or reanalyzed, since one or two of the three quality controls were outside the 10% acceptance range. However, it was decided that due to the low number of samples that were in question, the outcome of the population pharmacokinetic (PPK) analysis would most likely not be affected, therefore the PPK analysis was not repeated.

3.2. Simulations of free valproic acid concentrations

Since the free VPA concentration data from study M98-938 may or may not be reliable, it was important to see if one can predict free VPA concentrations from the Phase I study with different infusion rates, based on previous protein binding data. This may help validate the free VPA concentrations obtained in the population pharmacokinetic study (M98-938).

The sponsor was therefore requested to provide simulations of free plasma concentrations obtained after different infusion rates developed from data from a Phase I study (Study F90-182). The simulations were based on a model for the non-linear protein binding other than the relationship determined in Study M98-938.

The sponsor used a literature reference (Scheyer RD *et al*, Ther Drug Monit (1990) **12:**117-123), where the relationship between total and free VPA serum concentrations was determined in samples from 37 epileptic patients (total VPA concentration range 7.1-211.1 µg/mL). Scheyer *et al* used a reduced form of the two-binding site model where they assumed one-binding site to be saturable (i.e., nonlinear binding) and a second binding site to be nonsaturable. The authors used the following equation (solved for free VPA concentrations) for the relationship between free and total VPA concentrations:

$$free\ VPA = \frac{\sqrt{(P_S + K_D(1+r) - tVPA)^2 + 4K_D(1+r)\,tVPA} + tVPA - (P_S + K_D(1+r))}{2(1+r)}$$

where P_S is the concentration of serum binding sites (determined to 846 µM), K_D is the dissociation constant for the saturable binding site (determined to 70.6 µM), r is a constant ratio of bound to free VPA concentration for the nonsaturable binding (determined to 0.53) and *tVPA* is the total serum VPA concentration.

In study F90-182 (for design details, see section 1.1), 1000 mg eq. valproic acid was given as a 5-min, 10-min, 30-min or 60-min infusion to healthy male volunteers. Total VPA plasma concentrations were determined at the stop of infusion, and frequently during the initial decline of the plasma-concentration profiles and followed up to 72 h after start of infusion. The simulated free VPA concentration-time profiles during the first 2 hours are depicted in Figure 3.1.

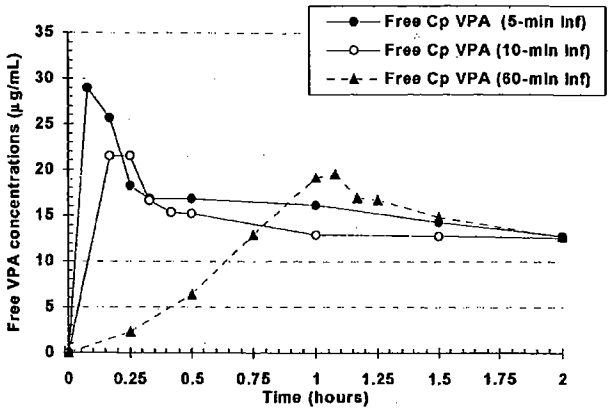


Figure 3.1 Simulated mean free VPA plasma concentration-time curves during the first 2 hours after 5 min (solid line with filled circles), 10 min (solid line with open circles) or 60-min (dashed line with triangles) i.v. infusions of 1000 mg to healthy volunteers (Study F90-182).

At infusion stop the simulated peak free VPA plasma concentrations were 51% higher after the 5-min infusion (C_{upred} 28.91 µg/mL), and 12% higher after the 10-min infusion (C_{upred} 21.56 µg/mL) compared to the 60-min infusion (C_{upred} 19.19 µg/mL). The mean observed total VPA concentration at infusion-stop after the 5-min infusion in healthy volunteers was 134 µg/mL. The mean total VPA plasma concentrations were 14% higher in the Phase I study (106 µg/mL) at the first comparable time-point, 15 min after infusion start, compared to study M98-938 (93 µg/mL). It should be noted that the differences in the free VPA plasma concentrations between the 5-min and 10-min infusions are transient, and are similar after 15 min, as observed in study M98-938.

Since no data is available on the long-term stability of the frozen plasma samples, a comparison was made by this reviewer between the observed mean free VPA concentrations and predictions of free VPA concentrations from the mean total VPA concentrations in Study M98-938, by use of the protein binding relationship by Scheyer *et al.* The predictions were almost identical, the difference between predicted and observed free VPA ranged from 0% to 12%. This finding supports the reliability of the pharmacokinetic estimates based on free VPA plasma concentrations from the PPK analysis.

In conclusion, although long-term stability data is pending, the sponsor adequately addressed the deficiencies regarding the bioanalytical methodology that were discovered during the DSI audit.

4. OVERALL COMMENTS TO THE MEDICAL OFFICER

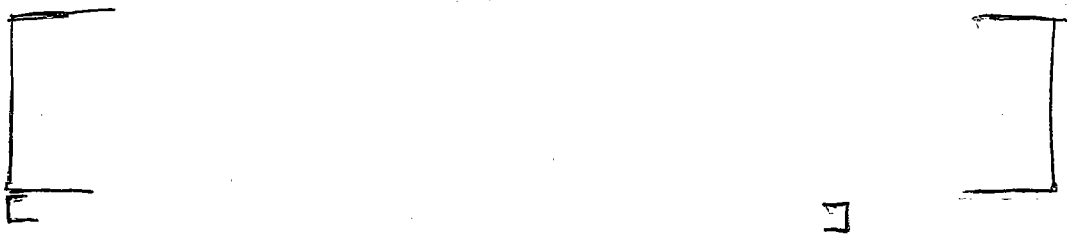
Population pharmacokinetic analysis (Study M98-938)

1. Due to the study design, it is difficult to compare the two infusion rates (15 mg/kg as a 5-min or 10 min infusion) during the time period where differences are most likely to occur, e.g. during the infusion and immediately after infusion stop. Although the total and free valproate plasma levels were comparable between infusion rates 15 min post-infusion, more information about potential differences would have been beneficial, to assess the influence of potential transient, high free drug concentrations on the pharmacokinetics of valproate during or at least, at the stop of infusion. Potential differences in the initial total and free drug concentrations between the two infusion rates may not have been captured.

2. The higher infusion rate (3.0 *vs.* 1.5 mg/kg/min eq. valproic acid) was associated with a somewhat higher free clearance of valproate compared to the slower rate of infusion (p=0.0665). Infusion rate also influenced total and free C_{max}.
3. Total clearance was estimated to be increased by 61% in patients that were metabolically induced, a corresponding increase of 23% in free clearance of valproate was determined. Metabolic induced status was assumed if the patient also was taking phenytoin, carbamazepine, and/or phenobarbital.
4. A Phase I study where corresponding VPA infusion rates (3.0 and 1.5 mg/kg/min) were given to healthy subjects showed that, at infusion stop, total VPA concentrations were 26% higher after a 5-min infusion and 6% higher after a 10-min infusion, respectively, compared to a 60-min infusion. Simulations of free VPA concentrations (phase I study) at infusion stop yielded 51% higher C_{max} after the 5-min infusion (C_{upred} 28.91 µg/mL), and 12% higher C_{max} after the 10-min infusion (C_{upred} 21.56 µg/mL) compared to the 60-min infusion (C_{upred} 19.19 µg/mL). The differences in the simulated free VPA plasma concentrations between the 5-min and 10-min infusions were transient, and returned to similar levels after 15 min, as observed in Study M98-938. The effect of these transient higher concentrations on safety is not known, and should be evaluated by the medical officer.
5. No relationship was observed between adverse events and VPA plasma concentrations. No analysis was performed due to the low incidence of adverse events.
6. The analysis of free valproic acid concentrations in Study M98-938 is deemed reliable in conjunction with the simulations and comparisons to literature data regarding the nonlinear protein binding relationship of unbound and total valproic acid. No long-term stability data of frozen plasma samples covering storage times used in this study is yet available.

Overall, clearance and C_{max} of valproate did not differ considerably between 3.0 *vs.* 1.5 mg/kg/min eq. valproic acid, given as a 5-min or a 10-min infusion, which may in part be related to the chosen study design. Safety concerns are likely to be related to the peak concentrations of free drug during and immediately after infusion-stop. Since the total and free C_{max} values of valproate were not captured, and only total concentrations were measured in the earlier traditional phase I study, the obtained pharmacokinetic data are of somewhat limited value. However, simulations provide some useful information (see comment 4 above).

A substantial part of the studied patient population had somewhat lower total valproate plasma concentrations compared to the healthy volunteers (data from the original NDA). This may indicate that the co-administration of known inducers (e.g. phenytoin) which was shown to increase both total and free CL of valproate, will distinctly influence the plasma drug profiles in patients.

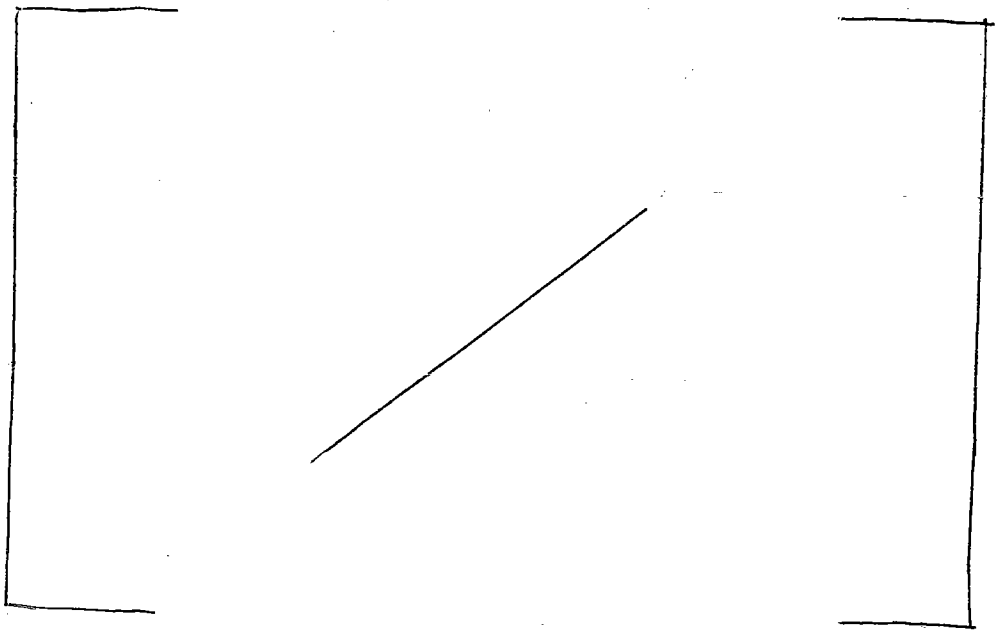


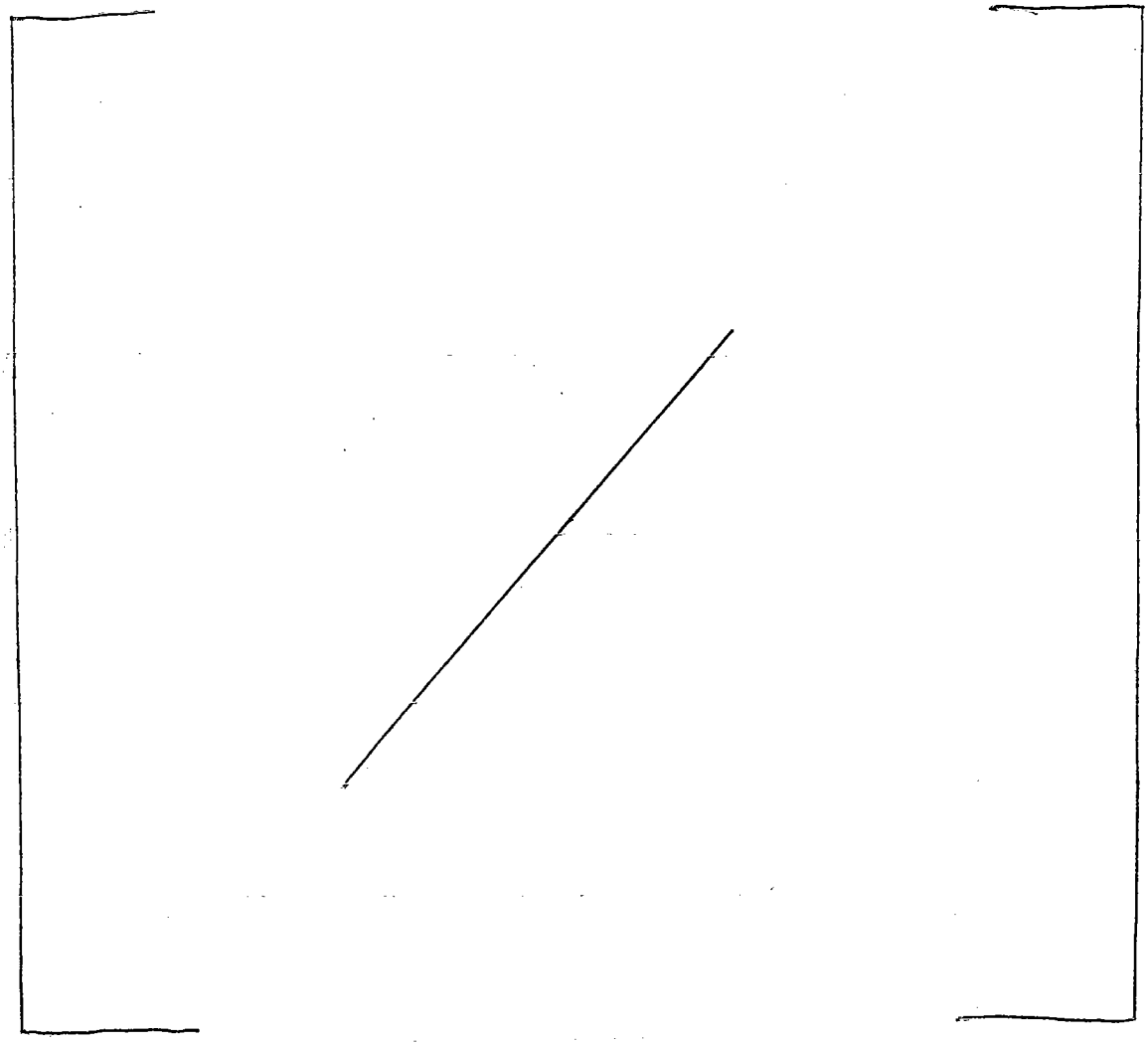
5. LABELING COMMENTS

The sponsor has proposed limited revisions of the text in the Clinical Pharmacology section of the approved label. The sponsor has added one paragraph and one figure to the CLINICAL PHARMACOLOGY Pharmacokinetics Bioavailability subsection, and has proposed a minor deletion in the Elimination subsection. One paragraph of the DOSAGE AND ADMINISTRATION section is also discussed in this review. Only the proposed revisions are included in this section, the sponsor's proposed label in full can be found in Appendix 2. The clinical sections of the label have also been updated (Pediatric use - number of patients updated, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

The sponsor has proposed the following revisions of the CLINICAL PHARMACOLOGY section (Recommended revisions by OCPB are marked as follows: *comments,* ~~deletions~~ or **changes**):

CLINICAL PHARMACOLOGY
Pharmacokinetics
Bioavailability





Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean terminal half-life for valproate monotherapy after [ ] intravenous infusion of 1000 mg was 16 ± 3.0 hours.

The sponsor has changed the wording in the 2nd sentence that previously read: 'Mean terminal half-life for valproate monotherapy after [ ] intravenous infusion of 1000 mg was 16 ± 3.0 hours.' This change is acceptable (data from study F90-182).
For the text of 2nd paragraph of this subsection, see Appendix 2.

DOSAGE AND ADMINISTRATION

Replacement therapy

When switching from oral valproate products, the total daily dose of DEPACON should be equivalent to the total daily dose of the oral valproate product (see CLINICAL

PHARMACOLOGY), and be administered as a 60 minute infusion [ ] [ ] with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary. Patients receiving doses near the maximum recommended daily dose of 60 mg/kg/day, particularly those not receiving enzyme-inducing drugs, should be monitored more closely. If the total daily dose exceeds 250 mg, it should be given in a divided regimen. However, the equivalence shown between DEPACON and oral valproate products (DEPAKOTE) at steady state was only evaluated in an every 6 hour regimen. Whether, when DEPACON is given less frequently (i.e., twice or three times a day), trough levels fall below those that result from an oral dosage form given via the same regimen, is unknown. For this reason, when DEPACON is given twice or three times a day, close monitoring of trough plasma levels may be needed. [ ]

[ ]

The corresponding text from the Clinical Pharmacology section has been added at the end of this paragraph.

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6. RECOMMENDATION

This supplemental NDA has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. From a pharmacokinetic point of view this supplemental NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Revisions of the sponsor's label are recommended. Please forward the proposed labeling revisions to the medical officer and sponsor as appropriate.

Maria Sunzel, Ph.D., Primary reviewer _____

Elena Mishina, Ph.D., Pharmacometrics specialist _____

RD/FT initialed by Ramana Uppoor, Ph.D., Team leader _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics
OCPB Briefing Date: April 9, 2001
Attendees: Drs. M Mehta, C Sahajwalla, R Uppoor, P Sheridan, J Feeney, N Nguyen and J DiGiacinto

c.c.: NDA 20-593/S-006, HFD-120 (Sheridan, Feeney), HFD-860 (Mehta, Uppoor, Mishina, Sunzel)

APPENDIX 1 PHARMACOMETRICS REVIEW

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 20-593/S-006 **Submission Date:** June 30, 2000
September 15, 2000
November 14, 2000
January 19, 2001

Drug Name:	Depacon (valproate sodium injections)
Formulation:	solution
Applicant:	Abbott Laboratories
Consult:	Report: "The Safety and Tolerance of Intravenous Depacon at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy."
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:
Valproate sodium for infusion (given during one hour) has been approved for the treatment of epilepsy. This supplemental submission is intending to evaluate the safety and tolerance of intravenous Depacon at the fast infusion rate (up to 3.0 mg/kg/min, or during 5-10 minutes) in subjects with epilepsy. The sponsor submitted for review the results and population data analysis of this study.

Objectives:
Primary: to evaluate the safety and tolerance of rapid infusion of intravenous Depacon at the rates of 1.5 mg/kg/min or 3.0 mg/kg/min, for a total dose of up to 15 mg/kg to an epileptic population.

Secondary: to evaluate the relationship between valproate administration and adverse events observed with this dosing strategy.

Objectives of the data analyses:

Compare Valproic acid (VPA) pharmacokinetics in subjects receiving Depacon at the rates of 1.5 vs 3.0 mg/kg/min, and in induced vs non-induced patients;
Determine predictors of Cmax and clearance as a function of demographics and dosing rate;
Identify significant factors affecting the binding of VPA to albumin;
Assess the accuracy of dosing and re-dosing strategy employed using subject's weight and an assumed population volume of distribution;
Evaluate the association of the adverse events with VPA plasma concentrations.

Methods:
Study Design:
It was an open label, prospective, randomized, Phase 3B, parallel group, multi-center trial with an infusion phase and an optional maintenance phase. Up to 4 infusions of Depacon were allowed in first 24 hours (total maximal dose per infusion was 15 mg/kg, with at

least 2 hours separating 2 infusions). After achieving the targeted plasma concentration, the patients were to receive oral valproate therapy for up to 14 days.
Patients in each center were randomized in a 2:1 ratio to receive 3.0 mg/kg/min or 1.5 mg/kg/min Depacon for a total dose of 15 mg/kg. Subjects were monitored for any adverse events during and after the infusion. Multiple blood pressure measurements (pre-infusion, 5, 10, 20, and 30 minutes post-infusion) were recorded and cardiac rhythm evaluations were performed during the infusion. Blood samples were taken up to 6 hours at various time points for the measurements of free and bound VPA in plasma. Plasma data were not collected during the maintenance phase. The patients returned to clinic 1 week after the final Depacon infusion for follow up and discussion of any adverse events. There were 13 sites in the US, and 112 patients with epilepsy were randomized and treated in the study.

Data Analyses:

Assay Method:

The [ ] analyzed plasma samples. Commercially available fluorescence polarization immunoassay has low limit of detection for total and free VPA in plasma of 12.5 and 2 mcg/mL, respectively.

Data:

Some data were censored from the data sets. All plasma concentration data from patients with total VPA pre-dose concentration ≥ 50 mcg/mL, and additionally few data points, which were considered as incongruous with concentrations, were not included in the analysis.

Comment: *The designation of the data points as the outliers was not based on any statistical test.*

Pharmacokinetic Analysis:

Noncompartmental analysis

For total and free VPA the applicant tabulated Cmax, calculated the area under the plasma concentration-time profile (AUCt), and presented the summary statistics for all patients. 96 patients were in the group, which had total dose of 15 mg/kg and no positive pre-dose VPA plasma concentrations. From this group, 54 patients received the dose over 5 minutes and 28 patients over 10 minutes; 52 patients had induced status, and 44 were not induced.

Population Analyses:

A total of 1498 VPA plasma concentrations from 109 subjects were used for [ ] analyses. Table 1 presents the results of both one and two compartmental model's runs for free and total VPA with and without the incorporation of the induction status. The random residual error model for both total and free VPA population models was assumed to be the sum of additive and proportional models.

$$Cp = F \cdot (1 + \varepsilon_1) + \varepsilon_2$$

where ε_1 and ε_2 are the proportional and additive error terms.

Table 1. Results of the Population Model Building

Run	Description	Objective Function	P-Value															
		Value		CL			V1			Q			V2			IND		
				Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE
1	Total-2CM	4447.678	<0.001	8.23	0.966	12	12.5	0.634	5	16.2	21.2	131	21.9	2.4	11			
2	Total-1CM	4595.563		1.52	0.131	9	12.1	0.365	3									
3	Free-2CM	1950.617	<0.001	15.6	2.68	17	74.1	5.14	7	32.0	5.72	18	52.4	11.4	22			
4	Free-1CM	2155.044		20.9	1.87	9	86.4	4.69	5									
5	Total-2CM+Ind	4446.858		8.32	1.04	13	12.6	0.708	6	16.6	2.39	14	22.4	2.81	13	0.258	0.525	203
6	**Total-1CM+Ind**	**4569.643**	**<0.001**	**1.21**	**0.085**	**7**	**12.3**	**0.373**	**3**							**0.739**	**0.241**	**33**
7	**Free-2CM+Ind**	**2149.042**	**>0.05**	**18.4**	**8.17**	**44**	**2.09**	**2.43**	**116**	**63.7**	**61.7**	**97**	**65.8**	**25.7**	**39**	**4.30**	**2.83**	**66**
8	Free-1CM+Ind	2144.612		17.6	2.57	15	87.2	4.76	5							5.76	4.24	74
9	Free-2CM*	2100.868		15.6	3.29	21	1.04	0.691	66	34.6	21.2	61	50.5	15.8	31			
10	Free-2CM+Ind*	2086.966	**<0.001**	13.6	2.53	19	1.00	0.575	58	32.5	17.5	54	48.8	13.9	28	3.34	2.14	64
				N1			K1			N2			K2			ETA(1)		
				Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE
1	1-site	-2186.710		1.49	0.0388	3	20.3	1.10	5							0.0731	0.0194	27
2	**2-site**	**-2199.79**	**<0.005**	**1.54**	**0.108**	**7**	**11.9**	**1.99**	**17**	**0.194**	**0.078**	**40**	**164**	**141**	**86**	**0.09**	**0.024**	**27**

continued

Run	ETA(1)			ETA(2)	
	Mean	SE	%SE	Mean	SE
1	41.0	19.9	49		
2	0.274	0.0466	17	0.182	0.161
3	0.771	0.246	32	0.434	0.114
4	0.360	0.0736	20	0.216	0.062
5	43.0	22.0	51		
6	**0.205**	**0.0530**	**26**	**0.168**	**0.117**
7	**0.560**	**0.560**	**100**	**0.037**	**0.046**
8	0.297	0.0903	30	0.225	0.072
9	0.354	0.180	51	0.040	0.038
10	0.297	0.130	44	0.042	0.035

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*Four data points (Subjects 212 at 0.0833 h, 213 at 0.1667 h, 805 at 0.0833 h, 913 at 0.0667 h) were excluded

Covariate Analyses:

The only covariate assessed by [ ] was the influence of the induction status on clearance of total and free VPA. The influence of all other covariates: age, weight, albumin, gender, lamotrigine, creatinine and dosing rate on Cmax, clearance, and protein binding constant K1 for both total and free drug were explored by the applicant with use of SAS analyses of variance.

Model Building and Validation:

Table 1 represents the population pharmacokinetic model building for total and free VPA. The validation of the models for the population data analyses with [ ] (pharmacokinetics and protein binding models) has not been described by the applicant.

Pharmacokinetic/Pharmacodynamic Analyses of Change in Blood Pressure:

SAS data analyses (ANOVA) were performed to explain the possible influence of the changes in blood pressure on demographic or pharmacokinetic factors. ANOVAs were performed for the analysis of the changes in systolic and diastolic blood pressure values from the baseline, with an initial model for the effects of weight, age, baseline and total or free VPA plasma concentrations. The data obtained at 5 minutes after infusion was used in the analyses. The effect was neglected in the model if the p values were larger than 0.1.

Results:

Data Collection:

The review of the submitted data revealed that the applicant did not take blood samples at the end of infusion. The Cmax values obtained by the applicant do not represent the true parameter estimates. This flaw in the study design led to ambiguous conclusions. For example, Cmax values presented in the report for the infusion rate of 1.5 mg/kg/min were greater on average than the same for 3.0 mg/kg/min infusion rate for the same administered dose of Depacon.

Noncompartmental Analysis:

The applicant compared the Cmax and AUCt values for two infusion groups. Because the concentration at the end of infusion was measured only in 2 patients, and on average plasma samples were taken about 12 minutes after the 5 minutes infusion, and 5.6 minutes after the 10 minutes infusion, the comparison of Cmax values cannot be performed in this setting. The AUCt values calculated for total and free VPA were similar for both infusion rates and induction status.

Population model:

Based on the Table 1, the sponsor selected one compartmental model for total VPA and two-compartmental model for free drug. In the justification for the choosing of these models the applicant referred to the estimations of clearance values which are close to the previously described literature values.

Model development shown in the Table 1 is not very convincing. The applicant argued that incorporation of the induction status as a covariate improved fit for the free drug.

Table 1 indicates the opposite: SE values of all parameters increased as well as the value of the objective function (run 7 vs run 3). Graphical assessment of the results of the population data analyses was not performed. The diagnostic plots prepared by FDA for free and total VPA indicate that both models have a room for improvement, especially for the free drug (Figures 1 and 2). The improvement of fit in [ ] usually is achieved by incorporation of the covariates into the model(s).
Error model development was not shown in the report.

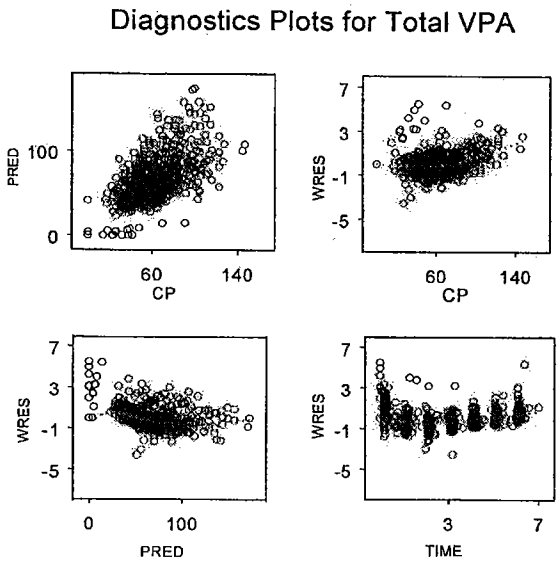

Figure 1. Diagnostics Plot for Total VPA

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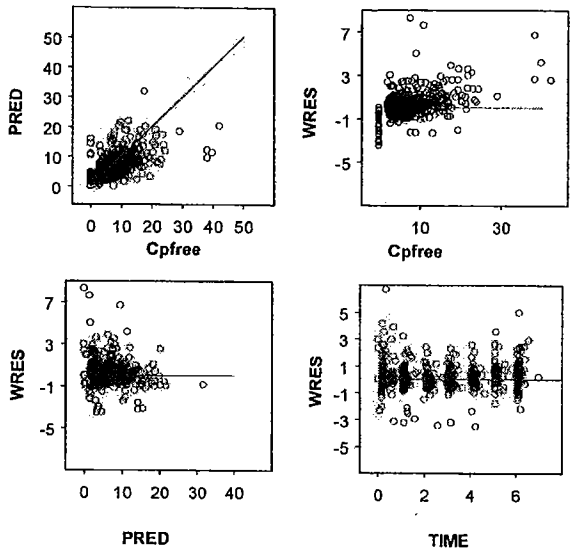

Figure 2. Diagnostics Plots for Free VPA

Covariate Analysis:

Please see the review of SAS data analyses by D. Schuirmann (please see Appendix). FDA performed graphical exploration of the influence of the covariates on the estimated pharmacokinetic parameters (clearance and volume of distribution of total and free VPA) based on [ ] output of the [ ] run presented by the applicant. The induction factor as well as gender effect seems to be influential on clearance but not on volume of distribution (Figure 3).

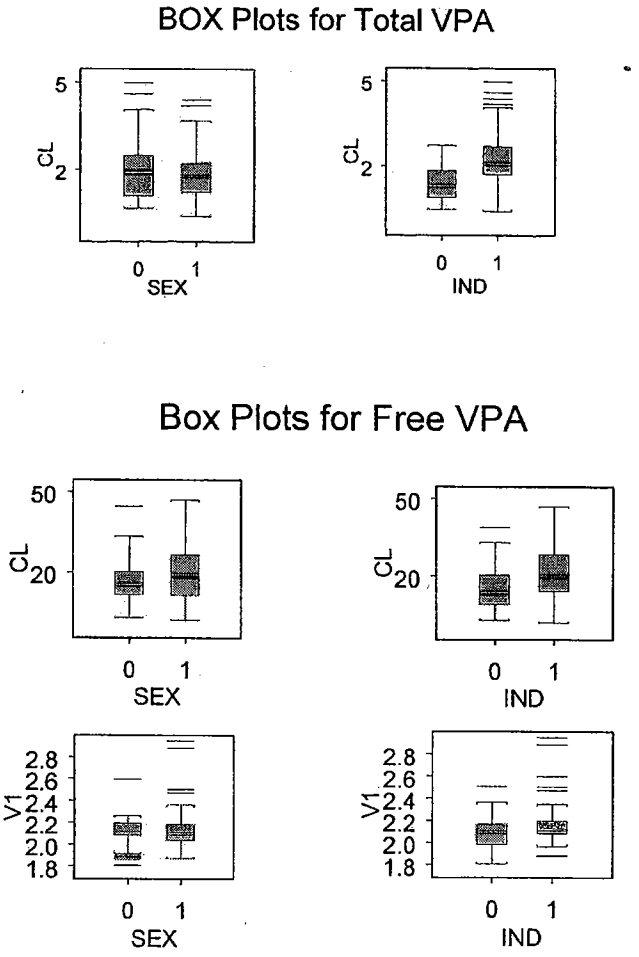

Figure 3. Box plots for the assessment of the influence of the induction status (0 - no induction, 1 - induction) and gender (0 - female, 1 - male) on clearance and volume of distribution of free and total VPA.

In the boxplots, the ends of the box are at the 1st and 3rd quartiles, the line is drawn at the median, the dark corridor shows the 90% confidence interval, and the lines outside the whiskers are the outliers.

Matrix plots (Figures 4 and 5) for both total and free VPA pharmacokinetic parameters show that the dependence of the clearance and volume of distribution on the following covariates: age, albumin (ALB), prothrombin index (TPRO), total bilirubin (TBIL), cholesterol (CHOL) and creatinine (CREA) was weak.

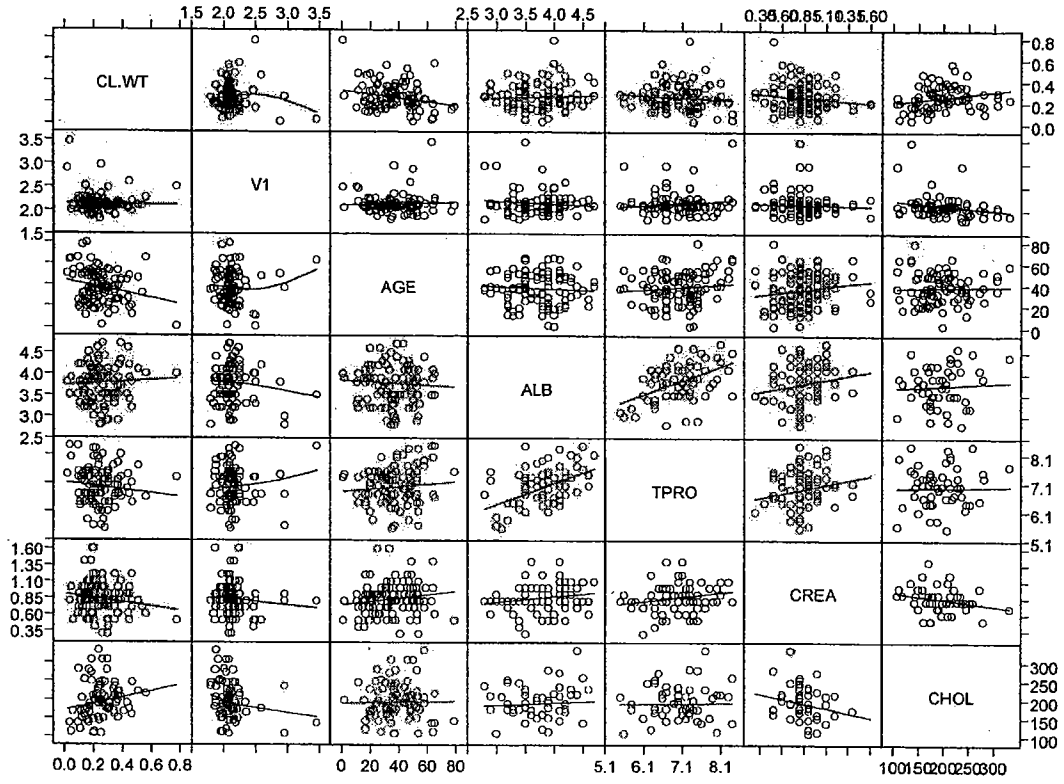

Figure 4. Total VPA pharmacokinetic parameters vs covariates. Lines are the smoothing splines.

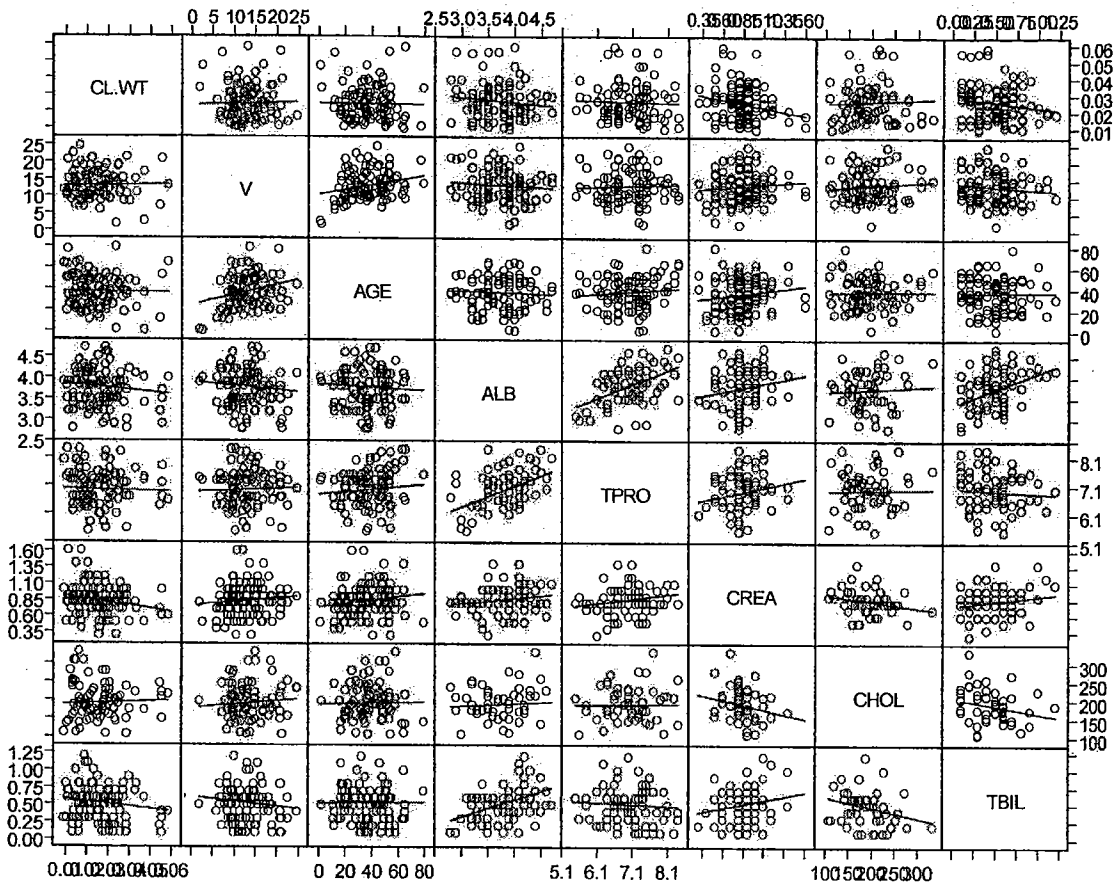

Figure 5. Free VPA pharmacokinetic parameters vs covariates. Lines are the smoothing splines.

Clearance Estimation: *Reported value for the total VPA half-life is in the range of 6-16 hours. In that experimental setting, the true values of clearance could not be estimated since samples were taken only up to 6 hours after infusion. Therefore, clearance estimation was not based on the terminal elimination phase.*

Protein Binding Model:
The applicant fitted one- and two-binding site models to the free and bound VPA plasma concentrations, and the latter model was selected as final. However, the difference in the objective functions between these models was marginal (13 units, $p<0.005$) and precision of the estimated parameters was worse for the chosen model. The applicant performed the covariate analysis using ANOVA, SAS (effect of cholesterol, creatinine, age, and

induction status) only for the K1 (please see the report of D. Schuirmann on the results of this analysis by SAS).
Additionally, the applicant described the relationship between total and free VPA plasma concentrations with polynomial function (plot is shown in the primary review). The purpose of modeling is to quantify the physiologic processes, and since such a model does not have any physiologic meaning the modeling is not very useful.

Pharmacokinetic/Pharmacodynamic Analyses of Change in Blood Pressure:

The applicant performed the regression analysis of changes in blood pressure data (information from the telecon with the applicant, November 30, 2000). The results of this analysis were not submitted for the review.
FDA plotted diastolic and systolic blood pressure vs free and total VPA plasma concentrations and analyzed the plots (Figure 6).

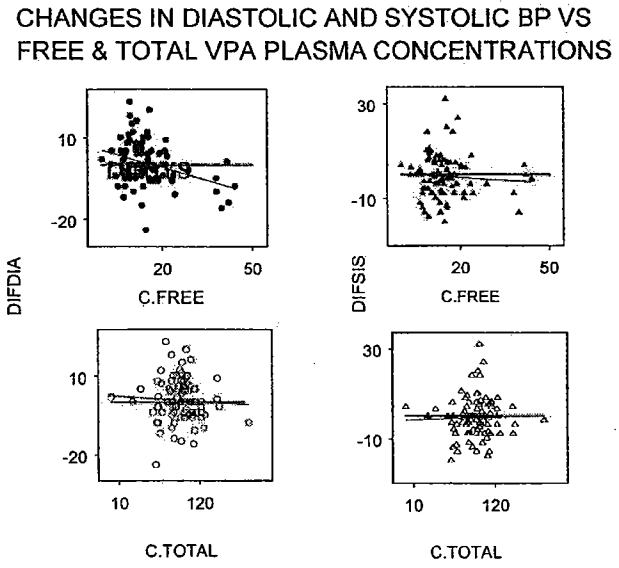

Figure 6. Changes in diastolic (DIFDIA) and systolic (DIFSIS) blood pressure (mm Hg) vs free (C.FREE) and total (C.TOTAL) VPA plasma concentrations. Thick lines show no change (the difference is equal to zero), thin lines are the result of the regression on the data points.

A shallow slope for the difference in the plot of diastolic blood pressure vs free VPA plasma concentrations was observed, and the changes were less for the higher free VPA in plasma. All plots show equal distribution of the data around the zero lines, it means that in this study, changes in systolic and diastolic blood pressure do not depend on either free or total VPA plasma concentration. Adverse effects on the cardiovascular system, i.e. hypertension, associated with VPA have previously been reported. In the present study, none of the infusions were stopped prematurely due to adverse events associated with blood pressure changes.

Evaluation of Adverse Events:

The relationship between adverse events and VPA plasma concentrations was compared for the infusion groups of 1.5 and 3.0 mg/kg/min of Depacon. Only adverse events during first 6 hours after the infusion were evaluated.

The incidence of adverse events was low, and no formal statistical analysis was performed. The majority of them were observed during the infusion in the initial phase of the study.

Comments:

1. The primary objective of this study was clinical safety and tolerance of rapid infusion of intravenous Depacon at the rates of 1.5 mg/kg/min or 3.0 mg/kg/min, for a total dose of up to 15 mg/kg to an epileptic population. This objective is assessed by the medical reviewer. The secondary objective 'to evaluate the relationship between valproate administration and adverse events observed with this dosing strategy' was not achieved. Since the incidence of adverse events was low, statistical evaluation of the relationship was not possible.

Only noncompartmental and [ ] data analyses are commented here. Please see comments on SAS data analysis in the report of D. Schuirmann.

2. The applicant did not take blood samples at the end of infusion. Cmax values obtained by the applicant do not represent the true parameter. This flaw in study design led to ambiguous conclusions. For example, Cmax values presented in the report for the infusion rate of 1.5 mg/kg/min were greater on average than the same for 3.0 mg/kg/min infusion rate for the same administered dose of Depacon. Although the Cmax comparison is not valid in this study, pharmacokinetics profiles for both rates of infusion seems to be similar. This is supported by the similar values of AUCt for both infusion rates.

3. Pharmacokinetic model development shown in the Table 1 is not very convincing. Graphical assessment of the results of the population data analyses was not performed. The FDA diagnostic plots for free and total VPA indicate that both models have a room for improvement, especially for the free drug (Figures 1 and 2). The improvement of fit in [ ] usually is achieved by incorporation of the covariates into the model(s). Only induction status was incorporated into the [ ] models. For the total VPA, the incorporation of the induction status significantly improved the fit (run 6 vs run 2), however, the same for the free drug made the fit much worse (run 7 vs run 3, SE values of all parameters increased as well as the value of the objective function). Deletion of the 'outliers', run 9 vs run 3 was not based on any statistical test and apparently did not improve the fit as well. Error model development was not shown in the report.

4. Model development for protein binding, Table 1, shows that the difference in the objective functions between the models with one and two binding sites was marginal (13 units, $p<0.005$) and precision of the estimated parameters was worse

for the chosen model. An attempt to describe the relationship between total and free VPA plasma concentrations using the polynomial function does not have any physiologic meaning.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the Report "The Safety and Tolerance of Intravenous Depacon at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy". The changes in Package Insert proposed by the applicant are acceptable with minor corrections (see Primary Reviewer's Labeling Comments).

_____ Date_____

Elena Mishina, Ph. D.
Pharmacometrics Specialist

_____

Ramana Uppoor, Ph. D.
Neuropharmacology Team Leader

cc list: NDA 20-593/S-006
Mehta, Uppoor, Sunzel, Mishina
BIOPHARM - CDR

APPENDIX

Statistical Review

Statistical Review: NDA 20-593/S-006, Depacon (valproate sodium injections), Abbott Laboratories

Material reviewed: Study report "The Safety and Tolerance of Intravenous Depacon® at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy" from NDA 20-593/S-006

The Sponsor carried out a study, described in the report "The Safety and Tolerance of Intravenous Depacon® at an Infusion Rate up to 3.0 mg/kg/min in Subjects with Epilepsy" (included in the Sponsor's submission). This was an open-label, prospective, randomized, Phase IIIB, parallel group, multi-center trial of intravenous Depacon® (valproic acid) in subjects with epilepsy. One hundred and twelve male and female subjects with epilepsy were randomized and treated in the study.

A number of statistical analyses were carried out, including analyses using [ ]
The subject of this review is the Sponsor's covariate analyses using SAS. For the responses log(Cmax) (observed Cmax from individual concentration-time profiles) and log(CL) (CL=clearance, post hoc estimates obtained from [ ]), for both free valproic acid (VPA) and total VPA, the report describes multiple regression models in which certain potential covariates – induction status, weight, age, albumin, gender, presence of lamotrigine, creatinine, and dosing rate - were examined as potential explanatory variables for the responses. Similarly for the response K_1 (protein binding constant, post hoc estimates from [ ] runs) induction status, cholesterol, creatinine, and age were considered as potential explanatory covariates. Elena V. Mishina, Ph.D. (pharmacometrics specialist in the Office of Clinical Pharmacology and Biopharmaceutics) requested an assessment of the appropriateness of the Sponsor's covariate analyses.

The Sponsor's covariate analyses examined the linear relationship between the response and the selected covariates. So long as it is appropriate to restrict attention to *linear* statistical models, use of SAS software such as SAS PROC GLM or SAS PROC REG, which utilizes small-sample test methods such as t-tests and F-tests, is as good as, and probably preferable to, nonlinear software such as [ ], which relies on large-sample, asymptotic methods such as likelihood ratio tests and Wald tests. Whether or not *nonlinear* models should have been considered for any of the potential covariates examined is beyond the scope of this review.

The problem faced by the Sponsor is described in the statistics literature as "selecting the 'best' regression." Various statistical methods have been proposed over the years for deciding which covariates to select, out of a pool of candidate covariates, which best achieve a balance between including covariates that improve the predictive power of the final regression model and not selecting covariates that produce little or no improvement in predictive power, producing the most parsimonious final model possible. Speaking about this statistical problem, Draper and Smith wrote:

> There is no unique statistical procedure for doing this, and personal judgment will be a necessary part of any of the statistical methods discussed.

(Draper, N.R., & Smith, H. (1966) **Applied Regression Analysis**, John Wiley & Sons, Inc., New York, 407pp.) The point is that there is no universally recognized "best" method for covariate selection.

A number of methods have been proposed over the years, most notably Forward Selection, Backward Elimination, Stepwise Regression, and Stagewise Regression. Descriptions of these methods may be found, for example, in standard texts such as Draper and Smith, or in the SAS documentation for PROC REG (in a volume such as SAS Institute Inc. *SAS/STAT™ User's Guide, Release 6.03 Edition*. Cary, NC: SAS Institute Inc., 1988. 1028pp.)

Based on the Sponsor's report, it was not clear what method of covariate selection was used. A telephone conversation was held at the request of Dr. Mishina. (See my memorandum of telephone conversation, attached to this review.) Based on this conversation it was apparent that the Sponsor used a version of the Forward Selection method. In this method, covariates are added to the model one at a time, based on which covariate provides the most statistically significant improvement to the fit of the model. Once the first covariate is chosen, other covariates are considered for inclusion in the model based on the improvement of fit they produce in a model that includes the first covariate selected. Covariates are sequentially added to the model in this fashion until none of the remaining covariates give a statistically significant improvement to the fit of the model (the Sponsor used a level of significance of 0.10.) In this case, the Sponsor forced one covariate, induction status, to be in all of the regression models, regardless of statistical significance. This was done for physiologic reasons.

It appears that the analysis of variance tables for the models finally selected are contained in Appendix D of the report. Based on those tables, the covariates selected were:

ln(Cmax) total VPA	induction status, weight, albumin, dosing rate
ln(Cmax) free VPA	induction status, weight, age, dosing rate
ln(CL) total VPA	induction status, weight
ln(CL) free VPA	induction status, weight, age, dosing rate
K_1	induction status, age

This list of covariates selected for each response is somewhat inconsistent with the Results and Discussion section of the Sponsor's report. Under the subheadings Predictors of C_{max} and Clearance:, C_{max}:, the report states "In this analysis, effects for previous experience with inducers, use of lamotrigine in the 3 days preceding study drug administration, weight and gender were not statistically significant ($p>0.1$)." This is true for Cmax both for total and free VPA, and yet in both cases induction status and weight were included in the final regression model (It is a feature of the Forward Selection method that a covariate may be entered into the model, and thus its contribution to the

model is statistically significant when it enters, but then other covariates added subsequently can make the contribution of covariates added earlier non-significant. This was the case for weight in both the total VPA and the free VPA ln(Cmax) analyses.) In the case of Clearance, the report states "In this analysis, effects for age, albumin, gender, presence of lamotrigine, creatinine and dosing rate were not statistically significant ($p>0.1$)." But in the analysis of variance table for ln(CL) for free VPA (Appendix D.2, page number 207 at the bottom of the page), the p-values for age and dosing rate are given as 0.0738 and 0.0665 respectively. This discrepancy is not explained.

The study was a multi-center trial, but the Sponsor presents no analyses designed to determine if the effects of covariates depend on the specific center.

Summary

1. The Sponsor's covariate analyses only considered linear relationships between covariates and response. This is not uncommon in exploratory analyses, since even nonlinear relationships might be expected to have a linear component. Nevertheless, the question of whether nonlinear models should have been considered for one or more of the candidate covariates is beyond the scope of this review.

2. Given that only linear relationships were considered, use of SAS procedures, such as SAS PROC GLM and SAS PROC REG, is appropriate.

3. The Sponsor appears to have used a version of the Forward Selection method of covariate selection (see attached memorandum of telephone conversation.) Other selection methods are available, but the Forward Selection method is well established, and no selection method has been identified as the "best" method to use. The Sponsor's choice, therefore, seems reasonable.

4. There is some inconsistency between the Sponsor's selected covariates, as given in Appendix D. of the report, and their Results and Discussion section. In particular, for ln(CL) of free VPA the effects of age and dosing rate are described as "not statistically significant ($p>0.1$)" in the Results and Discussion section of the report, but in Appendix D. the p-values are given as 0.0738 for age and 0.0665 for dosing rate.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods and Research Staff (HFD-705)

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:
Original NDA 20-593/S-006
HFD-860 Elena V. Mishina
HFD-860 Emmanuel Fadiran
HFD-705 Stella G. Machado
HFD-705 Donald J. Schuirmann
HFD-705 QMR Chron

Attachment - Memorandum of 12/21/00 Telephone Conversation

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On Original

Memorandum of Telephone Conversation

December 21, 2000 - 3:15pm to 3:38pm

between: representatives of Abbott Laboratories:
Steve Townsend (regulatory affairs)
Charles Locke (statistician)
Yi Ming Zhang (statistician)

and: Donald J. Schuirmann, Expert Mathematical Statistician, QMR Staff (HFD-705)

Subject: NDA 20-593/S-006 (Depacon)

The telephone conversation was held at the request of Elena V. Mishina, Ph.D. of the Office of Clinical Pharmacology and Biopharmaceutics. The subject was the method used for covariate selection in the analysis of a study of intravenous Depacon (valproate sodium injection) infusion rates, reported in NDA 20-593/S-006.

The report describes multiple regression models in which certain covariates – induction status, weight, age, albumin, gender, presence of lamotrigine, creatinine, and dosing rate - were examined to see if they were predictors of certain responses – the logarithms of observed Cmax for free valproic acid (VPA), observed Cmax for total VPA, Clearance (post hoc estimates from [ ] runs) for free VPA, and Clearance for total VPA. Similar analyses were carried out for the response K_1 (protein binding constant, post hoc estimates from [ ]) using induction status, cholesterol, creatinine, and age as potential covariates. I said that it was not clear from the study report how the firm had decided which covariates to include in the regression models. I noted that a rather long series of SAS statements had been provided by the firm, but that I could not determine the covariate selection method from examining these SAS statements.

Dr. Zhang indicated that they had tried using classic stepwise regression as implemented in SAS PROC REG, but that they were not satisfied with the resulting set of covariates on physiological grounds, based on consultation with other scientists at the firm. In particular, it was felt that induction status should be included in the regression models on physiological grounds. The firm decided to use the following strategy:

1. Candidate covariates were tried, one at a time, in a regression model that was forced to include induction status. If the improvement in the fit of the model was statistically significant (at the 0.10 level of significance) for a particular covariate, that covariate was added to the model.

2. Once a covariate was placed in the model, it stayed in the model. Subsequent candidate covariates were then tried in a model including any previously entered covariates.

3. Selection ceased when none of the remaining candidate covariates produced a statistically significant improvement in the model.

As stated in #2., once a covariate was entered into the model, it stayed in the model. This explains, for example, why in the final regression model for log Cmax for Total VPA (see Appendix D.1, APPENDIX PAGE 1, NDA 20-593/S-006 Vol 2 Pg 204) the p-value for the weight covariate is non-significant (p=0.1532). When weight was initially added to a model that had only induction status, it was significant, and so it was added to the model. When albumin and dosing rate were subsequently added to the model, weight was no longer significant, but was not removed.

The covariate selection method described by the firm appears to be a version of the *Forward* selection method, as implemented in SAS PROC REG. In the telephone conversation I did not determine whether the firm used SAS PROC REG, or whether they did the calculations "by hand". Dr. Zhang indicated that formal use of the *Stepwise* selection procedure, with induction status forced into the model, produced models very much like the ones reported. The firm did indicate that the long series of SAS statements, which make frequent calls to SAS PROC GLM, was used to produce display Analysis of Variance tables for inclusion in the study report, not to do the actual model selection.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods and Research Staff
Office of Biostatistics, CDER

25 page(s) of draft labeling has been removed from this portion of the review.

Clinical Pharmacology / Biopharmaceutics Review # 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maria Sunzel
4/17/01 02:47:54 PM
BIOPHARMACEUTICS

Elena Mishina
4/17/01 02:51:55 PM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
4/17/01 04:04:57 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-593/S-006	Submission Date: July 24, 2001
Name of Drug:	Depacon® Injection (valproate sodium) Injection for intravenous (IV) use: eq. 100 mg/mL valproic acid	
Indication of Drug:	Anti-epileptic (monotherapy or adjunctive therapy)	
Sponsor:	Abbott Laboratories, Abbott Park, IL 60064-6108	
Type of Submission:	Amendment to pending supplemental application	
Reviewer:	Maria Sunzel, Ph.D.	

Review of sponsor's counter-proposal of a new label for Depacon® Injection (valproate sodium).

This is a review of the sponsor's counter-proposal of a new label for Depacon Injection (valproate sodium) for intravenous (IV) use, submitted as an amendment to the pending supplement (S-006). The proposed label revisions are not fully satisfactory to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), and the review contains additional revisions and comments that are intended for the medical reviewer (page 2), and the sponsor's new label proposal (p 4-27).

Background
The sponsor submitted supplement S-006 which contained [redacted] The sponsor received an approvable letter (05/03/01), with label revisions to the proposed label (CPB review dated 04/17/01). Depacon Injection is approved for short-term IV use, up to 2 weeks of administration.

Major revisions in the sponsor's counter-proposal
(CLINICAL PHARMACOLOGY and DOSAGE & ADMINISTRATION sections)
The sponsor accepts the majority of the Agency's label revisions regarding the 'Clinical Pharmacology' sections of the label.

[redacted]

The sponsor's new label proposal is included in the Appendix 1 of this review (p 4-27).

Comments and suggested revisions to the sponsor's new label (July 20, 2001 version):
The sponsor has made minor editorial revisions, infusion rate, and dose clarifications to the CLINICAL PHARMACOLOGY section, which can be found in the Appendix of this review. These minor revisions are acceptable to the OCPB.

The sponsor has proposed the following revisions of the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections and recommended revisions by OCPB are marked as follows: ~~deletions,~~ **changes** or *comments*):

CLINICAL PHARMACOLOGY *(Appendix 1, page 5)*
Pharmacokinetics
Bioavailability

DOSAGE AND ADMINISTRATION *(Appendix page 25)*

Replacement Therapy: *(Appendix page 26, part of DOSAGE AND ADMINISTRATION)*

Conclusion:
All the sponsor's minor revisions are acceptable.

Recommendation:

The proposed label revision for Depacon® Injection (valproate sodium) is not fully satisfactory to the Office of Clinical Pharmacology and Biopharmaceutics. Please convey the conclusion, comments, and suggested revisions of the new label text to the medical reviewer.

Maria Sunzel, Ph.D. _____

RD/FT Initialed by Ramana Uppoor, Ph.D. _____

cc: NDA 20-593, HFD-120 (Ware, Sheridan, Feeney), HFD-860 (Mehta, Uppoor, Sunzel)

24 page(s) of draft labeling has been removed from this portion of the review.

Clinical Pharmacology/Biopharmaceutics Review #2

APPENDIX 2

Data from Study F90-197 (from sponsors original submission & CPB review dated 04/17/01):

TABLE 1. Pharmacokinetics (mean ± SD) of valproic acid in healthy male volunteers (n=15 per regimen) after the first and second oral dose intake. A 10-min i.v. loading infusion of 1000 mg eq valproic acid preceded the oral doses with 1 or 3 h. (Table identical to sponsor's table in the original NDA 20-593, submission date 03/17/1995, vol. 33, page 225.)

Parameter	Regimen					
	A: 500 mg q8h, 1 h after infusion-start		**B: 500 mg q8h, 3 h after infusion-start**		**C: 250 mg q6h, 1 h after infusion-start**	
	Oral 1*	Oral 2**	Oral 1*	Oral 2**	Oral 1*	Oral 2**
AUC (μg.h/mL)	642 ± 104	616 ± 108	530 ± 92	447 ± 107	473 ± 71	357 ± 63
C_{max} (μg/mL)	105 ± 17	68 ± 17	81 ± 13	71 ± 16	100 ± 21	69 ± 11
C_{min} (μg/mL)	61 ± 15	40 ± 10	54 ± 10	44 ± 12	63 ± 9	51 ± 10

*1st dose for Regimens A, B, C: AUC 1-9 h, 3-11 h, and 1-7 h, respectively. ** 2nd dose for Regimens A, B, C: AUC 9-17 h, 11-19 h, and 7-13 h, respectively

Trough plasma valproate concentrations for 3 days following the respective dosing regimens (see next page for tabulations of values):

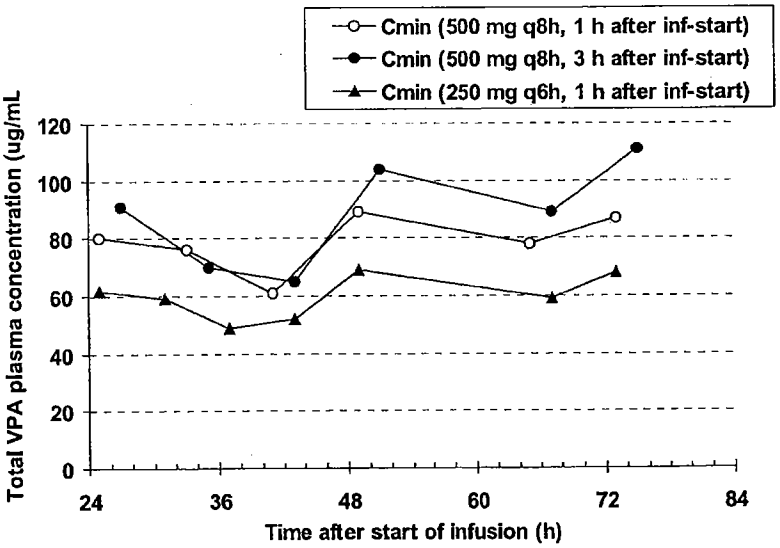

FIGURE 1. Total trough (average C_{min}) plasma concentrations after repeated oral doses of 500 mg eq valproic acid q8h (Dose 4-9), or 250 mg q6h (Dose 5-12) to healthy, male subjects (n=15/group). The first oral dose was given 1 or 3 h after an IV loading dose.

Table of the values depicted in Figure 1 (previous page), from the sponsor's original NDA 20-593, vol. 33, pages 226 (submission date 03/17/1995). Regimen A is 500 mg q8h initiated 1 h after infusion-stop; Regimen B is 500 mg q8h initiated 3 h after infusion-stop, and Regimen C is 250 mg q6h initiated 1 h after infusion-stop:

Day 3		Day 2				Day 3		Day 2			
Time (hr)	C_{min} (µg/mL)	Time (hr)	C_{min} (µg/mL)	% Diff.*	P Value	Time (hr)	C_{min} (µg/mL)	Time (hr)	C_{min} (µg/mL)	% Diff.*	P Value
Regimen A (q8h)						**Regimen B (q8h)**					
49	89 ± 18	25	80 ± 22	11.1	0.146	51	104 ± 22	27	91 ± 17	14.3	0.013
57	84 ± 25	33	76 ± 19	10.5	0.035	59	91 ± 15	35	70 ± 18	30.0	0.001
65	78 ± 19	41	61 ± 23	27.9	0.004	67	89 ± 18	43	65 ± 20	37.0	< 0.001
73#	87 ± 18	49	89 ± 18	-2.0	0.680	75#	111 ± 20	51	104 ± 22	6.8	0.149
73#	87 ± 18	65	78 ± 19	11.1	0.268	75#	111 ± 20	67	89 ± 18	24.7	< 0.001

Regimen C (q6h)					
49	69 ± 13	25	62 ± 15	11.3	0.096
55	65 ± 12	31	59 ± 13	10.2	0.001
61	62 ± 14	37	49 ± 11	26.5	0.001
67	59 ± 15	43	52 ± 14	13.5	0.004
73#	68 ± 15	49	69 ± 13	-1.4	0.888
73#	68 ± 15	67	59 ± 15	15.2	0.040

* % differences.
# Day 4 versus Day 3.

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On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maria Sunzel
11/20/01 11:27:37 AM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
11/20/01 12:21:03 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-593/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

(13.) PATENT INFORMATION

We Abbott Laboratories, certify that the drug Valproate Sodium Injection, "In the Applicant's opinion and to the best of the Applicant's knowledge, there are no U.S. Patents which claim the listed drug referred to in this Application or which claim a use for the listed drug for which Abbott Laboratories is seeking approval."

EXCLUSIVITY SUMMARY for NDA # 20-593 SUPPL # S-006
Trade Name Depacon Generic Name valproate sodium injection
Applicant Name Abbott Laboratories HFD- 120

Approval Date January 24, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE2

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-723 18-082

NDA # 19-680 21-168

NDA # 18-081

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # M98-938

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # ___M98-938

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 32,231 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Jackie Ware
Signature of Preparer Date
Title:

Russell Katz, Division Director
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jackie Ware
3/13/02 04:21:10 PM

Russell Katz
3/14/02 07:36:37 AM

Certification Requirement for all Applications

For Approval of a Drug Product

Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "A certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections(a) or (b) (Sections 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act), in connection with this application for approval of a drug product."

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

Steven E. Townsend

6/30/00

Steven E. Townsend
Associate Director, Pharmaceutical Products Division
Regulatory Affairs
Dept. 491, Bldg. AP6B-1
(847) 938-9547
100 Abbott Park Road
Abbott Park, Illinois 60064-6108

Date

Financial Disclosure by Clinical Investigators

Abbott Laboratories is submitting the following information under the provisions of 21 CFR 54.4. Provided in this section is a Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators covering clinical study M98-938.

This section is organized in the following manner:

- Form FDA 3454
  - List of names of clinical investigators meeting the requirements of 21 CFR 54.2(a), (b) and (f).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached List	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Lawrence E Roebel, Ph.D.	Vice President, PPD Regulatory Affairs and Research Quality Assurance
FIRM/ORGANIZATION	
Abbott Laboratories	
SIGNATURE	**DATE**
Lawrence E. Roebel	6/29/00

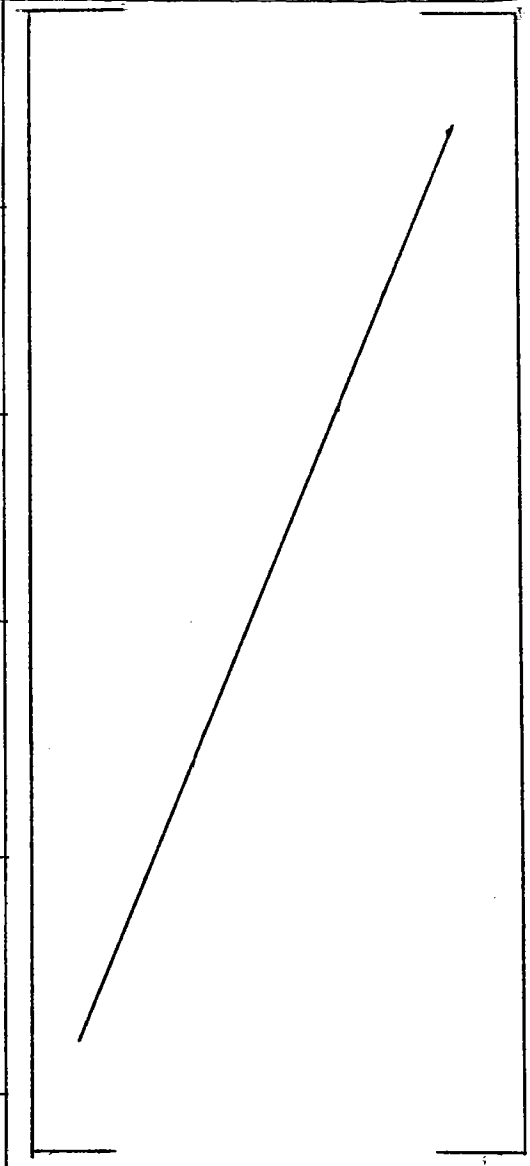
Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Study M98-938 Certification: Financial Interests and Arrangements of Clinical Investigators

Principal Investigator	Sub-Investigators / Coordinators
Cantrell Deborah T. Combs, MD (Investigator #14689, Site #9) North Texas Neuroscience Center 2001 N. MacArthur Blvd., Suite 500A Irving, TX 75061	
Cloyd James C, Pharm.D. (Investigator #14688, Site #3) University of Minnesota College of Pharmacy Wheaver Densford Hall, Room 7-101 308 Garvard St. SE Minneapolis, MN 55455-0353	
Gates, John R. MD (Investigator #6936, Site #1) Minnesota Epilepsy Group, PA 310 Smith Ave. North Suite 300 St. Paul, MN. 55102	
Kanner Andres M. (Andy), MD (Investigator #12696, Site #10) Rush-Presbyterian- St. Luke's Medical Center 1725 West Harrison Street Suite 755 PB Chicago, IL. 60612-3824	
Kuzniecky, Ruben I, MD (Investigator #4347, Site #11) University of Alabama Epilepsy Center 1719 6th Avenue S. CIRC 312 Birmingham, AL. 35294-0021	
Labiner David M. MD (Investigator #6984, Site #13) University of Arizona Department of Neurology 1501 North Campbell Avenue P.O. Box 245023 Tucson, AZ. 85724	
Montouris, Georgia D, MD (Investigator #7408, Site #4) The Comprehensive Epilepsy Center St. Luke's N. Medical Building 222 S. Woods Mill Rd. Suite 610 Chesterfield, MO 63017	

Principal Investigator	Sub-Investigators / Coordinators
Morris George L., MD (Investigator #5697, Site #12) Medical College of Wisconsin Department of Neurology 9200 West Wisconsin Avenue Milwaukee, WI 53226	
Naritoku Dean K., MD (Investigator #6688, Site #2) SIU School of Medicine Dept. of Neurology 751 N. Rutledge Springfield, IL 62794-1316	
Pellock John M. MD (Investigator #2529, Site #6) MCV/VCU Randolph Minor Hall-RM 702 307 College St. MCV Box 980211 Richmond, VA 23298-0211	
Ramsay, R. Eugene, MD (Investigator #2021, Site #7) University of Miami International Center for Epilepsy Professional Arts Building 1150 N. W. 14th St. Suite 410 Miami, FL 33136	
Vazquez, Blanca MD (Investigator #11430, Site #8) NYU -MT. Sinai School of Medicine 550 1st Avenue Rivergate Building New York, NY 10016	
Wheless, James W. MD (Investigator #14690, Site #5) The University of Texas Medical School at Houston Department of Neurology 6431 Fannin St. #7.044 Houston, TX 77033	

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-593 /SE2 - 006

Drug Depacon (valproate sodium injection) Applicant Abbott

RPM Ware Phone 4-5533

☒505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ☒S ☐P

Pivotal IND(s)

Application classifications:
Chem Class
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary 5/3/01
Secondary 7/3/01

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter ..... ☑AP ☑AE ☐NA (2nd / 1st)
- Labeling & Labels
  FDA revised labeling and reviews ..... ✓
  Original proposed labeling (package insert, patient package insert) ..... ✓
  Other labeling in class (most recent 3) or class labeling .....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☑ No
  Immediate container and carton labels ..... N/A
  Nomenclature review ..... N/A
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo) .....
  OC Clearance for approval .....

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter
- Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments
  - Copy of Applicant's commitments
- Was Press Office notified of action (for approval action only)? ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper
- Patent
  - Information [505(b)(1)] ✓
  - Patent Certification [505(b)(2)]
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]
- Exclusivity Summary ✓
- Debarment Statement ✓
- Financial Disclosure
  - No disclosable information
  - Disclosable information – indicate where review is located
- Correspondence/Memoranda/Faxes N/A
- Minutes of Meetings N/A
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference _____
- Advisory Committee Meeting N/A
  - Date of Meeting
  - Questions considered by the committee
  - Minutes or 48-hour alert or pertinent section of transcript
- Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X
- Clinical review(s) and memoranda X

Continued ⇨

- Safety Update review(s) ..... N/A

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... ✓
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda ..... N/A

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits X
  ☐Clinical studies ☑ bioequivalence studies .....

CMC INFORMATION: N/A

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda .....
- Statistics review(s) and memoranda regarding dissolution and/or stability .....
- DMF review(s) .....
- Environmental Assessment review/FONSI/Categorical exemption .....
- Micro (validation of sterilization) review(s) and memoranda .....
- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: N/A

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda .....
- Memo from DSI regarding GLP inspection (if any) .....

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... _____
- CAC/ECAC report ..... _____

Appears This Way
On Original

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, January 11, 2002 5:16 PM
To: Steve Townsend (E-mail)
Subject: Re: Depacon S-006


11102lbl_toAbbott.doc


Depacon S-006

Dear Steve,
I discussed your attached labeling proposal with Dr. Feeney today. After review, he asks that the words [ ] be deleted so that the phrase (in both places) would read as follows:

"...112 patients with epilepsy were given..." and "...approximately 90 patients with epilepsy and with no measurable plasma levels..."

A complete mark-up version is attached as a Word file.

Please let me know if this proposal is acceptable.

Thanks, Jackie
****

Jacqueline H. Ware, Pharm.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
301-594-5533 (phone)
301-594-2859 (fax)
warej@cder.fda.gov (email)

In a separate clinical safety trial, 112 [ ]patients with epilepsy [ ] [ ], were given -infusions of Depacon (up to 15mg/kg) over 5 to 10 minutes (1.5-3.0 mg/kg/min). The common adverse events (>2%) were somnolence (10.7%), dizziness (7.1%), paresthesias (7.1%), asthenia (7.1%), [ ]nausea (6.3%) and headache (2.7%). While the incidence of these adverse events was generally higher than in Table 1 (experience encompassing the standard, much slower infusion rates), e.g. somnolence (1.7%), dizziness (5.2%), paresthesia (0.9%), asthenia (0%), nausea (3.2%), and headache (4.3%) [ ], a direct comparison between the incidence of adverse events in the 2 cohorts cannot be made because of differences in patient populations and study designs.

DOSAGE AND ADMINISTRATION

DEPACON IS FOR INTRAVENOUS USE ONLY.

Use of DEPACON for periods of more than 14 days has not been studied. Patients should be switched to oral valproate products as soon as it is clinically feasible.

DEPACON should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary.

In one -clinical safety study, approximately 90 [ ]patients with epilepsy [ ] and with no measurable plasma levels of valproate were given single infusions of Depacon (up to 15mg/kg and mean dose of 1184mg) over 5-10 minutes (1.5-3.0mg/kg/min). Patients generally tolerated the more rapid infusions well (see Adverse Reactions [ ]). This study was not designed to assess the effectiveness of these regimens.

Ware, Jacqueline H

From: steven.e.townsend@secure.abbott.com
Sent: Friday, January 11, 2002 8:53 AM
To: WAREJ@cder.fda.gov
Subject: Depacon S-006

1-10-02 Draft Labeling.doc

Jackie,

Attached are some proposed changes to the draft labeling. I have used the
version of the labeling you provided on Monday and made the proposed changes
in red. After you have had a chance to look it over we can discuss it.

thanks,

Steve

(See attached file: 1-10-02 Draft Labeling.doc)
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"Abbott Laboratories Server <secmail1.cmis.abbott.com>"
made the following annotations on 01/11/02 07:53:08

[INFO] -- Access Manager:
This Message was sent by ABBOTT LABORATORIES across the Internet in
ENCRYPTED format and was successfully decrypted, unless otherwise noted.

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======

In a separate clinical safety trial, 112 [ ]patients with epilepsy [ ] [ ] were given -infusions of Depacon (up to 15mg/kg) over 5 to 10 minutes (1.5-3.0 mg/kg/min). The common adverse events (>2%) were somnolence (10.7%), dizziness (7.1%), paresthesias (7.1%), asthenia (7.1%), [ ]nausea (6.3%) and headache (2.7%). While the incidence of these adverse events was generally higher than in Table 1 (experience encompassing the standard, much slower infusion rates), e.g. somnolence (1.7%), dizziness (5.2%), paresthesia (0.9%), asthenia (0%), nausea (3.2%), and headache (4.3%) [ ], a direct comparison between the incidence of adverse events in the 2 cohorts cannot be made because of differences in patient populations and study designs.

DOSAGE AND ADMINISTRATION

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In one -clinical safety study, approximately 90 [ ] patients with epilepsy [ ] and with no measurable plasma levels of valproate were given single infusions of Depacon (up to 15mg/kg and mean dose of 1184mg) over 5-10 minutes (1.5-3.0mg/kg/min). Patients generally tolerated the more rapid infusions well (see Adverse Reactions [ ]). This study was not designed to assess the effectiveness of these regimens.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jackie Ware
1/14/02 10:35:28 AM
CSO

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, January 07, 2002 3:47 PM
To: Steve Townsend (E-mail)
Cc: Ware, Jacqueline H
Subject: NDA 20-593/S-006 draft labeling

Dear Steve,
Attached is the Division's proposed labeling for NDA 20-593/S-006. Please share it with the appropriate persons at Abbott and let me know if it is acceptable or if further discussion with us is needed.

Thank you in advance for your help!
Jackie

1702lbl sent to Abbott.doc

****

Jacqueline H. Ware, Pharm.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
301-594-5533 (phone)
301-594-2859 (fax)
warej@cder.fda.gov (email)

26 page(s) of draft labeling has been removed from this portion of the review.

Administrative and Correspondence : 1/7/02 Email

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jackie Ware
1/7/02 03:54:48 PM
CSO

Abbott Laboratories
Pharmaceutical Products Division
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Fax Transmittal Form

To: Jackie Ware
Company: Division of Neruopharmacological Drug Products
Telephone: 310-594-5533
Fax: 301-594-2859

From: Steven Townsend
Department: Regulatory Affairs
Telephone: (847) 938-9547
Fax: (847) 937-8068/(847) 937-8002
Date: 12-10-01

Total Pages: 4

Comments:

Jackie,

Attached is the AE table regarding the Depacon NDA 20-593/S-006. Please contact me if you have any questions.

Steve

ADVERSE EVENTS EMERGING FROM THE START OF THE FIRST INFUSION UP TO 24 HOURS FOLLOWING THE LAST INFUSION, OR WHICH WERE POSSIBLY OR PROBABLY STUDY DRUG RELATED GROUPED BY BODY SYSTEM, COSTART TERM AND SEVERITY

ALL SUBJECTS

BODY SYSTEM COSTART TERM&	COMBINED DEPACON GROUPS (N = 112) SEVERITY$				
	MILD	MOD	SEV	TOTAL	(%)
ANY ADVERSE EVENT	32	9	1	42	(37.50)
BODY AS A WHOLE					
ABDOMINAL PAIN	1	0	0	1	(0.89)
ASTHENIA	6	2	0	8	(7.14)
HEADACHE	2	1	0	3	(2.68)
INFECTION	0	1	0	1	(0.89)
INJECTION SITE INFLAMMATION	1	0	0	1	(0.89)
INJECTION SITE PAIN	2	0	0	2	(1.79)
INJECTION SITE REACTION	1	0	0	1	(0.89)
PAIN	1	0	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	13	3	0	16	(14.29)
CARDIOVASCULAR SYSTEM					
HYPOTENSION	1	0	0	1	(0.89)
VASODILATATION	1	0	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	2	0	0	2	(1.79)
DIGESTIVE SYSTEM					
DIARRHEA	1	0	0	1	(0.89)
DYSPEPSIA	2	0	0	2	(1.79)
DYSPHAGIA	0	1	0	1	(0.89)
NAUSEA	6	1	0	7	(6.25)
VOMITING	1	0	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	8	2	0	10	(8.93)

NOTE: TABLE DEPICTS THE MOST SEVERE ADVERSE EVENT FOR EACH COSTART TERM AS REPORTED FOR EACH SUBJECT.

& ADVERSE EVENTS WERE GROUPED INTO COSTART TERMS ACCORDING TO COSTART DICTIONARY VERSION V.
$ MILD = MILD, MOD = MODERATE, SEV = SEVERE.

Program Source Code: /guyihua/REQUEST01/05_12/938ae_24hr_rel_last.sas

ADVERSE EVENTS EMERGING FROM THE START OF THE FIRST INFUSION UP TO 24 HOURS FOLLOWING THE LAST INFUSION, OR WHICH WERE POSSIBLY OR PROBABLY STUDY DRUG RELATED GROUPED BY BODY SYSTEM, COSTART TERM AND SEVERITY

ALL SUBJECTS

BODY SYSTEM COSTART TERM&	COMBINED DEPACON GROUPS (N = 112) SEVERITY$				
	MILD	MOD	SEV	TOTAL	(%)
METABOLIC AND NUTRITIONAL DISORDERS					
WEIGHT GAIN	1	0	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	1	0	0	1	(0.89)
MUSCULOSKELETAL SYSTEM					
BONE DISORDER	0	1	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	0	1	0	1	(0.89)
NERVOUS SYSTEM					
ABNORMAL GAIT	0	2	0	2	(1.79)
DEPERSONALIZATION	1	0	0	1	(0.89)
DIZZINESS	8	0	0	8	(7.14)
ENCEPHALOPATHY	0	0	1	1	(0.89)
HYPESTHESIA	1	0	0	1	(0.89)
PARESTHESIA	8	0	0	8	(7.14)
SOMNOLENCE	10	2	0	12	(10.71)
SPEECH DISORDER	0	1	0	1	(0.89)
THINKING ABNORMAL	0	1	0	1	(0.89)
TREMOR	1	0	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	20	5	1	26	(23.21)
RESPIRATORY SYSTEM					
PHARYNGITIS	0	1	0	1	(0.89)
SUBJECTS WITH ONE OR MORE EVENTS	0	1	0	1	(0.89)

NOTE: TABLE DEPICTS THE MOST SEVERE ADVERSE EVENT FOR EACH COSTART TERM AS REPORTED FOR EACH SUBJECT.

& ADVERSE EVENTS WERE GROUPED INTO COSTART TERMS ACCORDING TO COSTART DICTIONARY VERSION V.
$ MILD = MILD, MOD = MODERATE, SEV = SEVERE.

Program Source Code: /guyihua/REQUEST01/05_12/938ae_24hr_rel_last.sas

ADVERSE EVENTS EMERGING FROM THE START OF THE FIRST INFUSION UP TO 24 HOURS FOLLOWING THE LAST INFUSION, OR WHICH WERE POSSIBLY OR PROBABLY STUDY DRUG RELATED GROUPED BY BODY SYSTEM, COSTART TERM AND SEVERITY

ALL SUBJECTS

BODY SYSTEM COSTART TERM&	COMBINED DEPACON GROUPS (N = 112) SEVERITY$				
	MILD	MOD	SEV	TOTAL	(%)
SPECIAL SENSES	1	0	0	1	(0.89)
AMBLYOPIA	2	0	0	2	(1.79)
TASTE PERVERSION					
SUBJECTS WITH ONE OR MORE EVENTS	3	0	0	3	(2.68)
UROGENITAL SYSTEM	1	0	0	1	(0.89)
HEMATURIA					
SUBJECTS WITH ONE OR MORE EVENTS	1	0	0	1	(0.89)

NOTE: TABLE DEPICTS THE MOST SEVERE ADVERSE EVENT FOR EACH COSTART TERM AS REPORTED FOR EACH SUBJECT.

& ADVERSE EVENTS WERE GROUPED INTO COSTART TERMS ACCORDING TO COSTART DICTIONARY VERSION V.
$ MILD = MILD, MOD = MODERATE, SEV = SEVERE.

Program Source Code: /guyihua/REQUEST01/05_12/938ae_24hr_rel_last.sas

ABBOTT

Pharmaceutical Products Division

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

July 24, 2001

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: Depacon®
Valproate Sodium Injection
NDA No. 20-593
Supplement No. S-006

Amendment to a Pending Supplemental Application:

Dear Dr. Katz:

The sponsor, Abbott Laboratories, submits the enclosed information under provisions of Section 505(b) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.110(a)(1), to amend supplemental new drug application (NDA 20-593/S-006) for Depacon® (Valproate Sodium Injection) in response to your May 3, 2001 action letter.

Reference is made to our June 30, 2000 submission, and our May 10, 2001 response indicating we would amend the application.

The purpose of this submission is to propose revisions to the draft labeling provided in the May 3, 2001 action letter. We acknowledge and concur with several of the comments provided in the action letter regarding the nature of the data provided by study M98-938 contained in supplement S-006. We would like to propose additional and alternative language which is based on data contained in our original March 20, 1995 NDA 20-593 submission and our June 30, 2000 supplement (S-006).

For ease of review, we have provided a table (Table 1) which contains the relevant portions of the non-highlighted version of the proposed labeling text, the corresponding FDA proposed and Abbott proposed text, and immediately adjacent comments/justifications for the proposed changes.

In addition, we are providing documentation (Table 2) requested in the May 3, 2001 action letter regarding how infusions where given at the sites that enrolled patients for study M98-938. Our investigation indicates that ten of the twelve sites administered the Depacon using an IV pump and two sites (Clody and Ramsey) utilized timed manual infusions.

Accordingly, enclosed are:

1. Table 1 (Proposed labeling changes with comments/justifications)
2. Table 2 (Study M98-938 Administration Method)
3. Proposed Draft Labeling (hard copy)
   a. Depacon Draft Label DN0623V5 July 20, 2001 with proposed additions/revisions/strikeouts
   b. Depacon Draft Label DN0623V5 July 20, 2001 Clean/Non-highlighted version
4. Proposed Draft Labeling (electronic version in Word 2000 (9.0.3821 SR-1))
   a. Depacon Draft Label DN0623V5 July 20, 2001 with proposed additions/revisions/strikeouts
   b. Depacon Draft Label DN0623V5 July 20, 2001 Clean/Non-highlighted version

Please note we do not consider the enclosed information to constitute a major amendment to this pending supplemental application. Should you have any questions or comments, please contact me at the number listed below.

Sincerely,

ABBOTT LABORATORIES

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET/vch
Enclosure

Copy of Submission to:
Jackie Ware, Pharm.D. Project Manager
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

111 page(s) of draft labeling has been removed from this portion of the review.

Administrative & Correspondence : 7/24/01

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2000

TO: File

FROM: Jackie Ware, Regulatory Project Manager

SUBJECT: **Tabular explanation of Population Pharmacokinetic Models**
NDA 20-593/S-006, Depacon Injection

During today's 3:00 p.m. (EST) teleconference between the Division's Clinical Pharmacology/Biopharmaceutics representatives and several Abbott representatives, it was agreed that the attached email and accompanying table should be sent to the NDA file for the above application. Specifically, the attached email contains Abbott's tabular explanation for the how the population pharmacokinetic models (discussed in the application) were developed. The Division's Clinical Pharmacology/Biopharmaceutics representatives agreed that Abbott did not need to make any additional submission related to the development of the population pharmacokinetic models for Depacon.

Printed by Jackie Ware

Electronic Mail Message

Date: 30-Nov-2000 12:03pm
From: Steven Townsend
steven.e.townsend@secure.abbott.com
Dept:
Tel No:

TO: warej (warej@A1)

CC: Verde Harper (Verde.Harper@ln.ssw.abbott.com)
CC: James Steck (James.Steck@ln.ssw.abbott.com)
Subject: Depacon Nov 30 Teleconference

Jackie,

Attached is a table that should be useful for discussing Model development this afternoon.

Steve

==========
"Abbott Laboratories Server <secmail1.cmis.abbott.com>"
made the following annotations on 11/30/00 11:03:17

[INFO] -- Access Manager:
This Message was sent by ABBOTT LABORATORIES across the Internet in ENCRYPTED format and was successfully decrypted, unless otherwise noted.

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Run	Description	Obj Func Value	P-Value	Parameters																	
				CL			V1			Q			V2			IND			ETA(1)			ETA(2)		
				Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE
1	Total-2CM	4447.678	<0.001	8.23	0.966	12	12.5	0.634	5	16.2	21.2	131	21.9	2.4	11				41.0	19.9	49			
																			0.274	0.0466	17	0.182	0.161	88
2	Total-1CM	4595.563		1.52	0.131	9	12.1	0.365	3										0.771	0.246	32	0.434	0.114	26
3	Free-2CM	1950.617	<0.001	15.6	2.68	17	74.1	5.14	7	32.0	5.72	18	52.4	11.4	22				0.360	0.0736	20	0.216	0.0624	29
4	Free-1CM	2155.044		20.9	1.87	9	86.4	4.69	5										43.0	22.0	51			
5	Total-2CM+Ind	4446.858		8.32	1.04	13	12.6	0.708	6	16.6	2.39	14	22.4	2.81	13	0.258	0.525	203						
																0.739	**0.241**	**33**	**0.205**	**0.0530**	**26**	**0.168**	**0.117**	**70**
6	**Total-1CM+Ind**	**4569.643**	**<0.001**	**1.21**	**0.0854**	**7**	**12.3**	**0.373**	**3**															
7	**Free-2CM+Ind**	**2149.042**	**>0.05**	**18.4**	**8.17**	**44**	**2.09**	**2.43**	**116**	**63.7**	**61.7**	**97**	**65.8**	**25.7**	**39**	**4.30**	**2.83**	**66**	**0.560**	**0.560**	**100**	**0.0372**	**0.0460**	**124**
8	Free-1CM+Ind	2144.612		17.6	2.57	15	87.2	4.76	5							5.76	4.24	74	0.297	0.0903	30	0.225	0.0727	32
9	Free-2CM*	2100.868		15.6	3.29	21	1.04	0.691	66	34.6	21.2	61	50.5	15.8	31				0.354	0.180	51	0.0409	0.0386	94
10	Free-2CM+Ind*	2086.966	**<0.001**	13.6	2.53	19	1.00	0.575	58	32.5	17.5	54	48.8	13.9	28	3.34	2.14	64	0.297	0.130	44	0.0421	0.0355	84

				N1			K1			N2			K2			ETA(1)		
				Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE	Mean	SE	%SE
1	1-site	-2186.710		1.49	0.0388	3	20.3	1.10	5							0.0731	0.0194	27
2	**2-site**	**-2199.787**	**<0.005**	**1.54**	**0.108**	7	**11.9**	**1.99**	**17**	**0.194**	**0.0783**	**40**	**164**	**141**	**86**	**0.0902**	**0.0242**	**27**

* Four datapoints (Subjects 212 at 0.0833 h, 213 at 0.1667 h, 805 at 0.0833 h, 913 at 0.0667 h) were excluded

/s/

Jackie Ware
12/27/00 03:31:24 PM
CSO