Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Divalproex Sodium
PRODUCT (Brand Name):	DEPAKOTE ER
NDA:	21-168 (SE5 015)
DOSAGE FORM:	Extended Release Tablet
DOSAGE STRENGTHS:	250 and 500 mg
INDICATION:	Treatment of Migraine and Epilepsy
NDA TYPE:	Pediatric Supplement in response to Pediatric Written Request
SUBMISSION DATES:	9/24/07
SPONSOR:	Abbott
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

This application is a prior approval supplement for Depakote ER extended release tablets. This submission supports safety labeling changes to incorporate labeling pediatric use information and also fulfills the Pediatric Written Request (PWR).

The PWR was initially issued on August 9, 2002 for the indications of migraine (age 12-17 years), epilepsy (age 3-10 years) and bipolar disorder (age 10-17 years). This PWR was further revised and reissued on January 31, 2006. The written request was amended to remove the requirement for efficacy study for epilepsy indication as the sponsor had made a good faith attempt to enroll patients into the clinical trial, but was not successful.

To obtain needed pediatric information on Depakote (valproate or VPA) delivered in various formulations, either as divalproex or valproic acid the PWR asked that information be submitted from studies in migraine prophylaxis, epilepsy and bipolar disorder. In addition, a literature review on VPA pharmacokinetic information in pediatric patients aged 3-10 years that included calculations on the age-appropriate dosing regimens was requested that includes the effect of covariates such as age, body weight etc and also concomitant medications in particular other anti-epileptics. A report on the spontaneous U.S. reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy in patients 3-10 years of age and 11-17 years of age was also requested.

The sponsor conducted a literature search and obtained 57 literature articles with pediatric pharmacokinetic information and has proposed 5 options for dosing recommendations as requested in the PWR, although the sponsor does not propose to add any dosing recommendation in the label for the epilepsy indication based on literature information and the lack of a successful effectiveness clinical trial. The clinical trial for migraine was also a failed trial. Labeling recommendation in the pediatric section related to safety is proposed by the sponsor.

1.1 RECOMMENDATION

The sponsor has completed the requirements of the Pediatric Written Request satisfactorily from a Clinical Pharmacology and pharmacokinetics perspective. Labeling changes for the "Highlights" section of the label for both Depakote ER and Depakote Sprinkle capsules have been made by this reviewer. The remaining sections of both the labels are acceptable as such without any changes and hence not given in this review. Please incorporate the labeling changes in the "Highlights" section of the label as given on page 10 of this review.

Note that no changes to the Pediatric pharmacokinetic and Dosing and Administration section of the label are being recommended (both by reviewer and sponsor).

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The literature review was conducted by the sponsor in Medline/PubMed using search phrases that included combinations of terms such as "VPA," "valproate," "pharmacokinetics," "child," and "pediatric." All search results were limited to human data and publications in English. The literature search was conducted for all available data, i.e., from 1965 to June 2007.

As per the Written Request, the published data provided information on the steady-state VPA maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to C_{max} (T_{max}), apparent volume of distribution (V_d/F), terminal phase elimination half-life ($t_{1/2}$), unbound fraction (F_u), and total and unbound clearances (CL and CL_u).

The literature articles provided by the sponsor have not been reviewed because an efficacy study was not successfully completed in this population because of enrollment issues and the sponsor is not seeking an indication for epilepsy in children age 3-10 years.

Sponsor's summary of the literature articles is summarized below. Depakote ER and Depakote Sprinkles were used in the pediatric studies described in this application:

Sponsor's Summary and Calculation of age appropriate regimens based on literature articles:

Sponsor's literature review identified seven reports of single dose pharmacokinetics of VPA in pediatric subjects with epilepsy on monotherapy (two reports; N=23) and polytherapy (i.e., enzyme-inducing concomitant medications; five reports; N=50). The doses ranged from 13 to 20 mg/kg for monotherapy and 3.2 to 21 mg/kg for polytherapy.

The steady-state pharmacokinetics of VPA have been extensively researched with 17 reports on pediatric subjects with epilepsy on monotherapy (N=341) and 13 reports on pediatric subjects with epilepsy on polytherapy (N=212). The doses ranged from 5.4 to 118 mg/kg/day for monotherapy and 15.1 to 150 mg/kg/day for polytherapy.

Individual VPA pharmacokinetic parameter values were available from 10 of the reports. These literature reports have spanned a wide array of VPA formulations including IV solution, oral solution, syrup, suppositories, sprinkle capsules, and capsules/tablets (immediate and delayed-release).

Table 1 summarizes the analysis resulting from the literature review performed on the pharmacokinetic parameters of VPA in children. A comparison with VPA pharmacokinetic parameters in adults is also presented. In addition, pharmacokinetic

parameters for VPA are described in the absence and presence of enzyme inducer AEDs.

Table 1. Literature-based Pharmacokinetic Parameters of Valproate in Children Aged 3 to 10 Years

		Enzyme Uninduced		Enzyme Induced	
Pharmacokinetic Parameter	**Units**	**Child**	**Adult**	**Child**	**Adult**
C_{max}/Dose	(μg/mL)/(mg/kg/day)	4.4	5.6	2.2	4.1
T_{max}	h	1 to 4	3.0	1 to 4	3.1
$t_{½}$	h	9 to 15	14 to 16	5 to 9	9 to 12
C_{min}/Dose	(μg/mL)/(mg/kg/day)	2.3	4.2	1.0	2.1
V_d/F	mL/kg	0.23	0.12 to 0.19	0.23	0.12 to 0.19
Unbound Fraction	%	5.8 to 22	7 to 30	5.8 to 22	7 to 30
Clearance	mL/h/kg	15.0	9.0	27.5	15.8
Unbound Clearance	mL/h/kg	132	90	225	158

Note: for further information on the contents of this table please refer to the to the Overview and Summary of Valproic Acid Pharmacokinetics in 3 to 10 Year-Old Children (R&D/07/646).

The only major difference in the ADME properties of VPA between adults and pediatric population identified in the literature is the rate of metabolism/elimination as characterized by clearance and the volume of distribution. Children, aged 3-10 years, have about 109% (3 years old) to 26% (10 years old) higher BW-normalized clearance compared with adults, reflecting the higher metabolic rate per kg BW in children typical for many drugs that are primarily eliminated by hepatic biotransformation.

This results in lower VPA concentrations in children, as characterized by Cmax and Cmin when equal BW- normalized doses are compared between the two age groups.

Children, aged 3-10 years, also have a slightly higher BW-normalized volume of distribution of 0.23 L/kg compared with adult values of 0.12 to 0.19 L/kg.

Accordingly, there is a trend toward a shorter half-life in children compared to adults; however, with widespread use of modified release formulations, and uncertainty from cross-study comparisons, the data are insufficient to suggest dosing frequency should be altered in children and adults. Other pharmacokinetic parameters like tmax and fraction unbound in plasma do not appear to be different between children and adults.

Effect of concomitant anti-epileptics on valproate plasma levels and vice versa are given in the following Tables:

Table: Effects of AEDs on VPA in children

AED	Effect on VPA	References
Carbamazepine	↓ 75%	Section 14.0
Phenytoin	↓ 75%	Section 14.0
Phenobarbital	↓ 75%	Section 14.0
Ethosuximide	↓ 28-37%	Salke-Kellermann 1997
Levetiracetam	↔	Fountain 2007

↑ Increase VPA AUC or concentration.
↓ Decrease VPA AUC or concentration.
↔ No change in VPA AUC or concentrations.

Among these AEDs, the only clinically relevant drug interactions with VPA include the decrease in total and unbound VPA concentrations due to enzyme induction by carbamazepine, phenytoin and Phenobarbital.

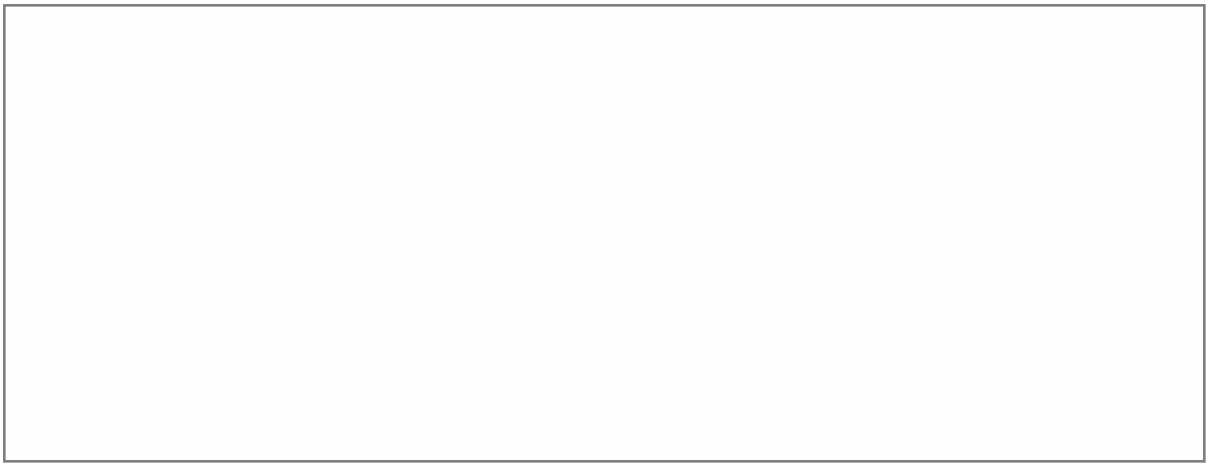
Table: Effects of VPA on AEDs in Children

AED	Effect on AED	References
Lamotrigine	↑ 85%	Vauzelle-Kervroedan 1996
Topiramate	↔	Adin 2004, Mikaeloff 2004
Felbamate	↑ 27%	Kelley 1997

↑ Increase VPA AUC or concentration.
↓ Decrease VPA AUC or concentration.
↔ No change in AED concentrations.

The effect of VPA coadministration on the pharmacokinetics of the above AED has clinical relevance for only lamotrigine.

Based on the pharmacokinetic modeling of the literature data, the sponsor has proposed 5 dosing options as per the PWR. The following 5 options for labeling have been recommended, though the sponsor does not wish to include any information in the labeling based on literature data.



Pages 6 through 7 redacted for the following reasons:
- -
Pages removed for the following reason:

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Ramana Uppoor, Ph.D._____

2.0 DETAILED LABELING RECOMMENDATION

Pages 10 through 12 redacted for the following reasons:
- -
Pages removed for the following reason:
draft labeling

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

/s/

Veneeta Tandon
1/14/2008 07:08:34 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
1/14/2008 11:56:50 AM
BIOPHARMACEUTICS