CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-168

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Ellen

Food and Drug Administration
Rockville MD 20857

Frederick G. Freitag, D.O.
Associate Director
Diamond Headache Clinic. Ltd.
467 West Deming Place
Chicago, Illinois 60614

MAY 18 2000

Dear Dr. Freitag:

Between March 7 and 17, 2000, Ms. Lisa Hayka representing the Food and Drug Administration (FDA), met with you and members of your staff to review your conduct of a clinical study (protocol M98-845) of the investigational drug divalproex sodium extended-release, performed for Abbott Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Hayka presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

> The informed consent document signed by subject 10822 failed to contain specific information on the potential teratogenic effects of the study drug, as required by the protocol.
>
> The Migraine Pilot Study Questionnaire was completed by subjects 10814, 10822, and 10826 prior to IRB approval of this document.
>
> Screening-visit progress note forms for all subjects were observed to contain a statement that anti-migraine medication was dispensed at screening, but the specific medication(s) and dosage(s) were not identified. We accept the response given by your Director of Clinical Research, ——— that these were erroneous, pre-printed entries and that no such medication was dispensed at screening.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: 3002962048
Field Classification: VAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
_____inadequate informed consent
_____inadequate drug accountability
__X__failure to adhere to protocol
__X__inadequate records
_____failure to report ADRS _____
__X__other: Failure to obtain IRB approval

cc:
HFA-224
HFD-132
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/Oliva
HFD-120 PM/Chen
HFD-120 Doc. Rm. NDA #21-168
HFD- 45 r/f
HFD- 47 c/r/s GCP file #10,033
HFD- 47 Lewin/Hajarian
HFR-CE650 DIB/Baumgarten
HFR-CE6520 BIMO Monitor/Yuscius
HFR-CE650 Field Investigator/Hayka

r/d:CL:05/11/00
reviewed:JAC:**(5/11/00)**
f/t:mb:**(5/17/00)**

o:\cl\FreitagApr00VAI.doc

Note to Rev. Div. M.O.

This routine data audit was conducted in support of pending NDA 21-168 and focused on the conduct of protocol M98-845. Twenty-six (26) subjects enrolled at this site; eighteen (18) subjects completed; and eight (8) subjects discontinued (6 withdrawals due to time constraints, 1 screen failure, and 1 withdrawal due to lack of efficacy). There were no serious adverse events noted.

Records for all subjects were reviewed. Significant inspectional observations are noted in the foregoing letter. There were no inspectional observations that would adversely impact the acceptability of the data generated at this site.

Data appear acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Chen

Food and Drug Administration
Rockville MD 20857

Paul K. Winner, D.O.
Premiere Research Institute
5205 Greenwood Avenue, Suite 200
West Palm Beach, Florida 33407

MAY 19 2000

Dear Dr. Winner:

Between February 22 and 24, 2000, Ms. Brunilda Torres representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol M98-845) of the investigational drug divalproex sodium extended-release, performed for Abbott Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written response dated February 29, 2000, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Torres presented and discussed with you the finding listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not follow the proper randomization procedure in the assignment of randomization numbers 22406, 22407, 22408, 22409, 22410, 22411, 22415, and 22416. We accept your explanation regarding this observation and note that you appear to have adequate measures in place to prevent recurrence of this finding in any ongoing or future studies.

We appreciate the cooperation shown Investigator Torres during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301) 594-1032.

Sincerely yours,

/S/

for Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: 3002923417
Field Classification: VAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required (responded)
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
_____inadequate informed consent
_____inadequate drug accountability
__X__failure to adhere to protocol
_____inadequate records
_____failure to report ADRS _____
_____other

cc:
HFA-224
HFD-132
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/Oliva
HFD-120 PM/Chen
HFD-120 Doc. Rm. NDA #21-168
HFD- 45 r/f
HFD- 47 c/r/s GCP file #9965
HFD- 47 Lewin/Hajarian
HFR-SE250 DIB/Chappell
HFR-SE2585 BIMO Monitor/Torres

r/d: CL:05-12-00
reviewed:JAC:**(5/19/00)**
f/t:mb:**(5/19/00)**

o:\cl\Winner May00VAI.doc

Note to Rev. Div. M.O.

This routine data audit was conducted in support of pending NDA 21-168. Twenty-three (23) subjects were enrolled in study M98-845 at this site, fifteen (15) of whom completed the study. Eight (8) subjects discontinued, for the following reasons: unable to come for study visits (2), excessive use of symptomatic medication (2); excessive use of symptomatic medication and chest pain (1); screen failure (1); and non-compliance (1). No serious adverse events were noted. Records for six (6) subjects were reviewed.

The inspection found that Dr. Winner violated the protocol by failing to follow the randomization procedure when assigning randomization numbers for eight subjects, as noted in the accompanying letter. The sponsor was notified of this finding while monitoring the study and reportedly classified these subjects as non-evaluable. All but one of these improperly randomized subjects completed the study; subject 22411 was discontinued after Visit 6, for chest pain and overuse of other anti-migraine medication.

Data appear acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-120
Chen

Food and Drug Administration
Rockville MD 20857

APR 11 ''

Edward Westbrook, M.D.
Associate Director of Neurology
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, Ohio 44106

Dear Dr. Westbrook:

Between February 23 and 29, 2000, Ms. Karen M. Kondas, representing the Food and Drug Administration (FDA), met with you and members of your staff to review your conduct of a clinical study (Protocol M98-845) of the investigational drug Depakote ER (divalproex sodium extended release) Tablets, performed for Abbott Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. However, the informed consent document used in this study did not disclose alternative courses of treatment that might be advantageous to potential subjects. This information is required by Part 50.25 of our regulations (copy enclosed). Please note item (a) 4.

We appreciate the cooperation shown Investigator Kondas during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely,

/s/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Enclosure:
#1 Part 50.25

FEI: 3002930036
Field Classification: NAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

The informed consent deficiency noted in the foregoing letter was not brought to Dr. Westbrook's attention during the inspection.

Deficiencies noted:
__X__inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
____inadequate records
____failure to report ADRS _____
____other

cc:
HFA-224
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/Oliva
HFD-120 PM/Chen
HFD-120 Dcc. Rm. NDA #21-168
HFD- 45 r/f
HFD- 47 c/r/s GCP file #9964
HFD- 47 Lewin/Hajarian
HFR-CE450 DIB/Fielden
HFR-CE450 BIMO Monitor/Grelle
HFR-CE4525 Field Investigator/Kondas
r/d: cl:04-10-00
reviewed:AEH:**(4/10/00)**
f/t:mb:**(4/10/00)**
o:\cl\Westbrook Apr00VAI.doc

Note to Rev. Div. M.O.

Twenty-two (22) subjects were screened at this site, two (2) of whom were screen failures. Twenty (20) subjects enrolled; nineteen (19) subjects completed the study; and one (1) subject withdrew due to an adverse event (hives) which was reported to be unrelated to study drug. Records from ten (10) subjects were reviewed in the course of this routine data audit. There were no deaths or other serious adverse experiences noted. All adverse experiences were reported to the sponsor.

Data appear acceptable.

ABBOTT

Pharmaceutical Products Division

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

October 20, 1999

Ms. Lana Chen, Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration, CDER
1451 Rockville Pike
Rockville, MD 20852

RE: Depakote ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168

GENERAL CORRESPONDENCE
Desk Copies

Dear Ms. Chen:

Reference is made to your October 14 and 15, 1999 requests for information, regarding Depakote ER (Divalproex Sodium Extended-Release) Tablets (NDA 21-168). In accordance with your request, we are providing, herewith, twelve desk copies of volume 1 of the above referenced New Drug Application (NDA), submitted September 30, 1999. These copies are duplicates of the previously submitted volume, for your reference. Please note that the Debarment Statement and Patent Information requested are contained in the Forms section and Section 13.0, respectively of volume 1. In addition, enclosed are two copies of the list of investigators and subinvestigators for Study M98-845. The remaining requested information will be provided, when available.

Should you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547/Fax: (847) 937-8002

SET/vh
Enclosures

M98-845 Investigators and Subinvestigators

Sheena K. Aurora, M.D.
Henry Ford Hospital
Department of Neurology
2799 West Grand Blvd., K-11
Detroit, MI 48202

Jeffrey Baggish, M.D.
(Replaced by Dr. Yataco 11/98)
Innovative Medical Research
1001 Crowell Bridge Road, Suite 300
Towson, MD 21286 100

Raymond Brewer, M.D.
Texas Headache & Pain Management
1804 NE Loop 410, Suite 100
San Antonio, TX 78217

Roger Cady, M.D.
Headache Care Center
1230 East Kingsley
Springfield, MO 65804

John W. Cochran, M.D.
VNC Neuroscience Center, LTD
4660 Kenmore Avenue #1018
Alexandria, VA 22304

James J. Corbett, M.D.
University of Mississippi Medical Center
Department of Neurology
2500 North State Street
Jackson, MS 39216-4505

Keith B. Edwards, M.D.
Neurological Consultants, P.C.
140 Hospital Drive, Suite 210
Bennington, VT 05201

Frederick G. Freitag, D.O.
Diamond Headache Clinic
467 West Deming Place
Chicago, IL 60614

Jerome Goldstein, M.D.
The San Francisco Headache Clinic
909 Hyde Street, Suite 230
San Francisco, CA 94109

Robert G. Kaniecki, M.D.
Allegheny Neurological Associates
420 East North Avenue, Suite 206
Pittsburgh, PA 15212

Jack A. Klapper, M.D.
Colorado Neurology and Headache Center
1155 East 18th Avenue
Denver, CO 80218

David Kudrow, M.D.
California Medical Clinic for Headache
16500 Ventura Blvd., Suite 245
Encino, CA 91436

Robert Kunkel, M.D.
Cleveland Clinic Foundation
Headache Center
9500 Euclid Avenue, Suite 91
Cleveland, OH 44195

Herbert G. Markley, M.D.
UMass - Memorial Health Care
Memorial Hospital
119 Belmont Street
Worcester, MA 01605

Ninan T. Mathew, M.D.
Houston Headache Clinic
1213 Hermann Drive, Suite 350
Houston, TX 77004

Joseph A Nicolas, M.D.
(Replaced Dr. Ramadan 03/99)
Cincinnati Headache Clinic
222 Piedmont Avenue, Suite 3200
Cincinnati, OH 45129-4217

Nabih Ramadan, M.D.
Cincinnati Headache Clinic
222 Piedmont Avenue, Suite 3200
Cincinnati, OH 45129-4217

John Rothrock, M.D.
University of South Alabama
Department of Neurology
2451 Fillingim Street, MSCB 1155
Mobile, AL 36617

Joel R. Saper, M.D.
Michigan Head Pain
& Neurological Institute
3120 Professional Drive
Ann Arbor, MI 48104

Fred D. Sheftell, M.D.
The New England Center for Headache
778 Long Ridge Road
Stanford, CT 06902

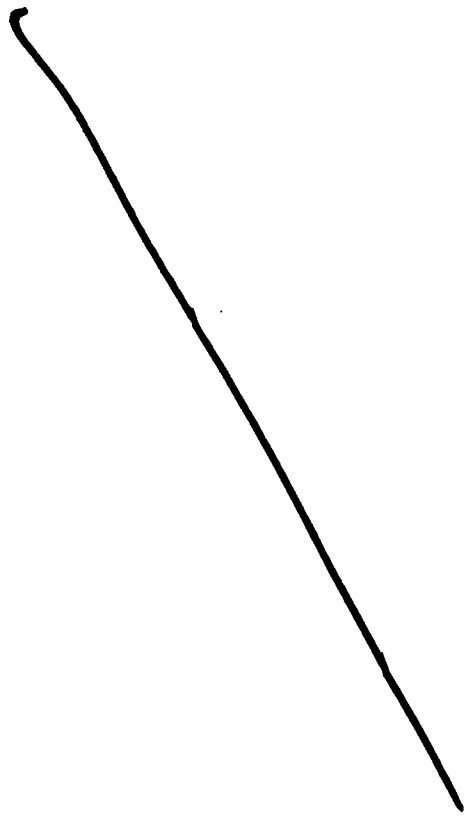
Stephen Silberstein, M.D.
Jefferson Headache Center
111 S. 11th Street #8130
Philadelphia, PA 19107

Egilius L.H. Spierings, M.D., Ph.D.
Boston Clinical Research Center
25 Walnut Street, Suite 102
Wellesley Hills, MA 02181

Jerome M. Walker, M.D.
Neurology & Headache Specialists
of Atlanta, LLC
2665 North Decatur Road, Suite 630
Decatur, GA 30033

Edward Westbrook, M.D.
University Hospitals of Cleveland
Division of Clinical Research,
Lakeside 5512
11100 Euclid Avenue
Cleveland, OH 44106

Paul K. Winner, D.O.
Premiere Research Institute
Palm Beach Neurological Group
5205 Greenwood Avenue, Suite 200
West Palm Beach, FL 33407



Alberto Yataco, M.D.
(Replaced Dr. Baggish 11/98)
Innovative Medical Research
1001 Crowell Bridge Road, Suite 300
Towson, MD 21286

M98-845 Investigators and Subinvestigators

Sheena K. Aurora, M.D.
Henry Ford Hospital
Department of Neurology
2799 West Grand Blvd., K-11
Detroit, MI 48202

Jeffrey Baggish, M.D.
(Replaced by Dr. Yataco 11/98)
Innovative Medical Research
1001 Crowell Bridge Road, Suite 300
Towson, MD 21286 100

Raymond Brewer, M.D.
Texas Headache & Pain Management
1804 NE Loop 410, Suite 100
San Antonio, TX 78217

Roger Cady, M.D.
Headache Care Center
1230 East Kingsley
Springfield, MO 65804

John W. Cochran, M.D.
VNC Neuroscience Center, LTD
4660 Kenmore Avenue #1018
Alexandria, VA 22304

James J. Corbett, M.D.
University of Mississippi Medical Center
Department of Neurology
2500 North State Street
Jackson, MS 39216-4505

Keith B. Edwards, M.D.
Neurological Consultants, P.C.
140 Hospital Drive, Suite 210
Bennington, VT 05201

Frederick G. Freitag, D.O.
Diamond Headache Clinic
467 West Deming Place
Chicago, IL 60614

Jerome Goldstein, M.D.
The San Francisco Headache Clinic
909 Hyde Street, Suite 230
San Francisco, CA 94109

Robert G. Kaniecki, M.D.
Allegheny Neurological Associates
420 East North Avenue, Suite 206
Pittsburgh, PA 15212

Jack A. Klapper, M.D.
Colorado Neurology and Headache Center
1155 East 18th Avenue
Denver, CO 80218

David Kudrow, M.D.
California Medical Clinic for Headache
16500 Ventura Blvd., Suite 245
Encino, CA 91436

Robert Kunkel, M.D.
Cleveland Clinic Foundation
Headache Center
9500 Euclid Avenue, Suite 91
Cleveland, OH 44195

Herbert G. Markley, M.D.
UMass - Memorial Health Care
Memorial Hospital
119 Belmont Street
Worcester, MA 01605

Ninan T. Mathew, M.D.
Houston Headache Clinic
1213 Hermann Drive, Suite 350
Houston, TX 77004

Joseph A Nicolas, M.D.
(Replaced Dr. Ramadan 03/99)
Cincinnati Headache Clinic
222 Piedmont Avenue, Suite 3200
Cincinnati, OH 45129-4217

Nabih Ramadan, M.D.
Cincinnati Headache Clinic
222 Piedmont Avenue, Suite 3200
Cincinnati, OH 45129-4217

John Rothrock, M.D.
University of South Alabama
Department of Neurology
2451 Fillingim Street, MSCB 1155
Mobile, AL 36617

Joel R. Saper, M.D.
Michigan Head Pain
& Neurological Institute
3120 Professional Drive
Ann Arbor, MI 48104

Fred D. Sheftell, M.D.
The New England Center for Headache
778 Long Ridge Road
Stanford, CT 06902

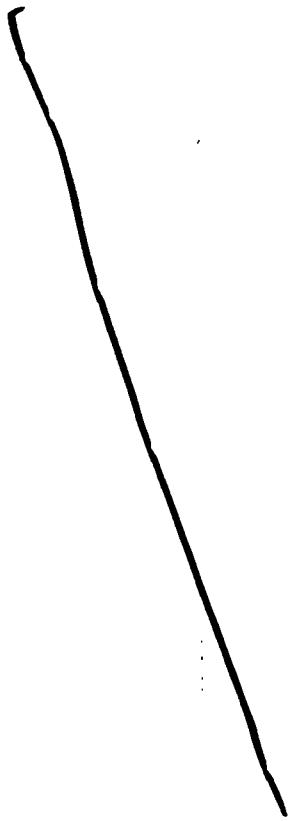
Stephen Silberstein, M.D.
Jefferson Headache Center
111 S. 11th Street #8130
Philadelphia, PA 19107

Egilius L.H. Spierings, M.D., Ph.D.
Boston Clinical Research Center
25 Walnut Street, Suite 102
Wellesley Hills, MA 02181

Jerome M. Walker, M.D.
Neurology & Headache Specialists
of Atlanta, LLC
2665 North Decatur Road, Suite 630
Decatur, GA 30033

Edward Westbrook, M.D.
University Hospitals of Cleveland
Division of Clinical Research,
Lakeside 5512
11100 Euclid Avenue
Cleveland, OH 44106

Paul K. Winner, D.O.
Premiere Research Institute
Palm Beach Neurological Group
5205 Greenwood Avenue, Suite 200
West Palm Beach, FL 33407



Alberto Yataco, M.D.
(Replaced Dr. Baggish 11/98)
Innovative Medical Research
1001 Crowell Bridge Road, Suite 300
Towson, MD 21286

ABBOTT

Pharmaceutical Products Division

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

January 17, 2000

Constance Lewin, M.D.
Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Room 125
Rockville, MD, 20855

RE: Depakote ER®
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168

General Correspondence
Response to FDA Request for Information

Dear Dr. Lewin:

Reference is made to your original January 10, 2000 request and our subsequent January 12, 13, and 14, 2000 telephone conversations regarding Study M98-845 contained in our New Drug Application for Depakote ER Tablets for Migraine (NDA 21-168) submitted September 30, 1999.

Accordingly enclosed, in four volumes, is the following requested information:

Volume Number	Description of Information	Appendix Number/Title/Subject Number	Page Number
1	Primary Efficacy Data (Investigators: Freitag, Saper, Westbrook, Winner, and Speirings)	Calculated 4-Week Headache Rates Appendix 16.2_3.2 Visit Data Excluded from Efficacy Analysis Appendix 16.2_6.1.1 Headache Report Data	001B 003 004
1	Discontinued Patients (all investigator sites)	Appendix 16.2_1.1 Study Summary Subset for Subjects who Did not Complete Study Through Visit 7	123
1	Adverse Events (all investigator sites)	Appendix 16.2_7.1.1 Adverse Events Appendix 16.2_7.1.2 Serious Adverse Events	150 288
1	Randomization Schedule (all investigator sites)	Baseline and Randomized Patient Numbers	291

Volume Number	Description of Information	Appendix Number/Title/Subject Number	Page Number
2	Case Report Forms (Freitag)	Subject 2 Subject 7 Subject 16	001 064 130
2	Case Report Forms (Saper)	Subject 5 Subject 9 Subject 11	189 258 329
3	Case Report Forms (Westbrook)	Subject 1 Subject 12 Subject 15	001 062 146
3	Case Report Forms (Winner)	Subject 4 Subject 8 Subject 11	206 269 330
4	Case Report Forms (Speirings)	Subject 2* Subject 3 Subject 4* Subject 8	001 002 059 060

* Patient not randomized.

Should you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Steven E. Townsend

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547
Fax: (847) 937-8002

SET/vh
Enclosures

Copy of this Cover Letter to:
Ms. Lana Chen, Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

ABBOTT

Pharmaceutical Products Division

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

July 14, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration, CDER
1451 Rockville Pike
Rockville, MD 20852

**RE: Depakote ER®
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168**

**GENERAL CORRESPONDENCE:
Response to FDA Request for Information**

Dear Dr. Katz:

The purpose of this submission is to provide a response to an FDA request for information regarding the *in-vitro in-vivo* correlation (IVIVC) provided in the September 30, 1999 original NDA submission for Depakote ER (Migraine).

Reference is made to a July 10, 2000 telephone conversation with Maria Sunzel, Ph.D., of the Division of Pharmaceutical Evaluation I, regarding determination of the internal predictability for C_{max} and AUC for the three formulations used to establish the IVIVC and to provide the prediction errors in percentages.

Accordingly enclosed is the requested information.

Internal Consistency of IVIVC model.

For both AUC and C_{max} we have determined % prediction errors, with predicted values obtained from the IVIVC model and the *in vitro* dissolution rates for slow-releasing, to-be-marketed, and fast-releasing formulations and with reference values taken to be the geometric means observed in Study M95-414. Please note that these simulations are based on the approach used to establish the setting of specifications provided in our September 30, 1999 original NDA submission (Section 6.16, Volume 16, Page 208). Please also recall that the IVIVC model was obtained from Study M95-414 in an analysis of *in vitro* and *in vivo* data with the NONMEM program. The regression model obtained for the IVIVC is the basis of the simulations.

The regression equation obtained for the IVIVC model was:

$$\text{Absorption Rate} = 8.73 + 0.900 \bullet (\textit{In Vitro}\ \text{Rate})$$

To evaluate the internal consistency of the model, STELLA (version 5.1.1) simulations were conducted based on the above equation. Therefore, for the convolution, the *in vitro* rates were simulated as zero order processes obtained from the regression slopes of the percent dissolved vs. time data, which had the following estimates:

Formulation	Rate (mg/h)
A (slow)	22.34
B (reference)	28.37
C (fast)	44.84

The intercept from the NONMEM analyses was simulated as release over a 3-hour period with the following code:

Intercept: if time < 3 then 0.0873•dose/3 else 0
Absorption rate (mg/h) = Intercept + 0.900 • *in vitro* rate

As noted previously, in addition to the IVIVC regression equation, it was also necessary to take into account the observation from Study M95-414 that the faster-dissolving ER formulation had an apparently greater AUC than the reference or slow-dissolving ER. From the least squares means of the analysis of the logarithm of AUC, the absolute bioavailability of the slow ER was 0.879, and for the fast ER was 1.004. The absolute availability of the formulations was thus based on the interpolation equation:

$$F = [\ 1.00 - (0.121/22.5) \bullet (44.84 - \textit{in vitro}\ \text{rate})]$$

As was done for the simulations to assist in the proposal of specification limits, the values of the dispositional pharmacokinetic parameters used in the simulation of the regimens were obtained from the mean elimination rate constant (0.046 h^{-1}) and mean distribution volume (10.24 L) obtained from the reference intravenous regimen. With these values of the elimination rate constant and distribution volume, the AUC for the IV reference is 1061.5 µg•h/mL, which is within 4% of the geometric mean observed value (1103.1 µg•h/mL).

The results of the STELLA simulations for the ER regimens A (slow dissolution), B (to-be-marketed) and C (fast dissolution) are listed below along with the geometric mean observed C_{max} and AUC values♦:

	A (slow)	B (ref)	C (fast)	Mean
AUC_∞ predicted				
AUC_∞ observed				
% Absolute Error				3.35
C_{max} predicted				
C_{max} observed				
% Absolute Error				5.83

As can be seen from the results above, the mean absolute prediction errors for AUC and C_{max} were 3.4 and 5.8%, respectively, and there were no errors for individual formulations that were —— %. From these results and the previously outlined summary statistics of the NONMEM IVIVC analyses, we believe future projections based on the model should be robust and accurate.

We trust that the above provides the information requested during the July 10, 2000 telephone conversation. Should you have any questions regarding this submission, please contact me at the number listed below. In addition, we are interested in learning if the revised dissolution specifications for Depakote ER tablets provided in our September 30, 1999 original NDA submission referenced above are acceptable.

Sincerely,

Steven E. Townsend

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547
Fax: (847) 937-8002

SET/vh

♦ The geometric mean pharmacokinetic variables from Study M95-414 may be found in Appendices D.2 and D.3 of report R&D/96/425 (NDA 21-168, Section 3.4.6.4, Volume 7, Pages 146 – 157).

Copy of this Submission to:

Ms. Lana Chen, R.Ph., Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

Maria Sunzel, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I
Woodmont II, HFD-860
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Abbott Laboratories	DATE OF SUBMISSION July 14, 2000
TELEPHONE NO. *(Include Area Code)* (847) 938-9547	FACSIMILE (FAX) Number *(Include Area Code)* (847) 937-8002
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 100 Abbott Park Road D-491/AP6B-1 Abbott Park, IL 60064-6108	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-168

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Divalproex Sodium Extended-Release Tablets	PROPRIETARY NAME *(trade name)* IF ANY Depakote ER Tablets
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Sodium Hydrogen bis (2-propylpentanoate)	CODE NAME *(If any)* None

DOSAGE FORM. Tablet	STRENGTHS: 500 mg	ROUTE OF ADMINISTRATION Oral

(PROPOSED) INDICATION(S) FOR USE:
Migraine

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED n/a

THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Depakene Capsules - NDA No. 18-081; Depakene Syrup - NDA No. 18-082; Depakote Tablets - NDA No. 18-723; Depakote Sprinkle Capsule, 125 - NDA No. 19-680; Divalproex Sodium Tablet, NDA No. 20-320; IND No. —

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
✔	20. OTHER *(Specify)* Response to FDA Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Steven E. Townsend	Steven E. Townsend, Associate Director, PPD Regulatory Affairs	July 14, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
100 Abbott Park Road D-491/AP6B-1 Abbott Park, Illinois 60064-6108	(847) (847) 938-9547

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

NDA No. 21-168
Depakote ER
(divalproex sodium extended-release)

Location of Manufacturing, Packaging and Control Sites for Divalproex Sodium Extended-Release Tablets Drug Substance

Abbott Laboratories
1401 Sheridan Road
North Chicago, Illinois 60064

Location of Manufacturing, Packaging and Control Sites for Depakote ER (divalproex sodium extended-release) Tablets

Abbott Laboratories
KM. 58, Carretera 2
Cruce Davila, Barceloneta
Puerto Rico 00614

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064

In addition to control testing at these sites, finished dosage form and stability testing is carried out at:

Abbott Laboratories
1401 Sheridan Road
North Chicago, Illinois 60064

ABBOTT

Pharmaceutical Products Division

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

April 28, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration, CDER
1451 Rockville Pike
Rockville, MD 20852

RE: Depakote ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168

GENERAL CORRESPONDENCE:
M98-845 Patient Diary Information

Dear Dr. Katz:

The purpose of this submission is to provide the Study M98-845 patient diary information as requested during our February 14, 2000 teleconference. As indicated in our February 23, 2000 proposal provided by facsimile to Ms. Lana Chen, of your staff, this submission contains hard copies of the patient diaries and SAS transport files of requisite headache event data on CD-ROM for the 64 randomly selected patients. In addition, to understand the impact of applying the FDA provided algorithm, we have completed an evaluation of the headache data and are providing our results and conclusions for consideration.

Data Collection

In order to meet the Division's request for diary data in electronic format for the subset of 64 randomly selected patients (based on the patient selection method outlined in our February 23 proposal), the following activities occurred: source data acquisition, subset database creation, data entry and verification, and subset database merge with original NDA Case Report Forms (CRFs) data.

Based on the example of a migraine algorithm provided in the February 23 facsimile from Ms. Chen, of your staff, all information necessary for classification was not present on CRFs. Therefore, the primary or source documentation (i.e. patient diaries) had to be obtained from each of the investigator sites. All patient event diaries were photocopied and submitted to Abbott. The headache attributes coded as "characteristics" per International Headache Society (IHS) criteria (ref. Cephalalgia 8: (Suppl 7) 1988), as well as the symptom of aura, were double-key entered into a unique diary database for this subset of patients. Manual review of the data points was performed in order to verify patient entry of a "characteristic" or aura into a diary matched with investigator review and commentary of those same event characteristics

(e.g., Dr. Klapper's subject 11111 reported aura as a symptom, but site comments contained in the diary specified it was not a true aura, therefore "aura" was not included in the database). It should be noted that diaries were completed daily; for headaches that spanned more than one day, subjects often recorded the symptoms and characteristics experienced each day. Therefore, if a subject recorded differing headache attributes on various days for the same headache, all unique attributes were entered into the database. If multiple intensities were reported for the same headache, the worst intensity was data-entered. Diary entries were matched to the CRF headache entries by date-time of headache onset. In the few cases where a perfect match was not found in date-time, the match was confirmed by a manual review of the symptoms and other information reported on the CRF and in the diary. This exercise also confirmed all headache events included in the original NDA for these 64 subjects and did not disclose any additional headaches during the study.

Dataset

The dataset being provided on CD-ROM contains details of all 1176 headache events recorded on the CRFs for the 64 selected patients. Each record of the dataset provides the details of a single headache event and includes the information previously provided from the "Headache Report" CRFs (i.e., dataset 'HQ: Headache Diary' submitted with the original NDA) plus additional migraine headache attributes collected in the patient diaries, but not reported on the "Headache Report" CRFs. Among the included variables relevant to assessing the headache attributes against the FDA provided algorithm, there were two sources of data. Data obtained from the CRFs included: the headache type and the symptoms of nausea, vomiting, photophobia, phonophobia, and other symptoms for headaches coded as migraines. Diaries provided the symptom of aura and the following headache characteristics for all headaches: headache intensity, unilateral, bilateral, worse with movement, pulsating, steady, or other characteristics.

Electronic Data Format

The CD-ROM contains four files: m2hq.xpt, datatoc.pdf, define.pdf and blankcrf.pdf. The m2hq.xpt file is a Version 5 SAS Transport File containing the dataset described above. The datatoc.pdf file is a simple table of contents file that links to the define.pdf file. The define.pdf file lists and defines the M2HQ dataset variables. Note that these variables and definitions are identical to those included in the HQ dataset in the original submission, with the addition of eight variables found in the diaries but not on the CRF referenced above. These additional variables begin with 'M2' rather than 'HQ'. The define.pdf file contains annotated images of both the subject diary and the previously submitted CRF.

Evaluation of Data

In order to understand the impact of applying the FDA provided algorithm for classification of individual headaches in migraine study, we did an analysis using the algorithm applied to all migraine headaches reported by the 64 patients. Headache episodes were classified using the FDA provided algorithm and the requirement that subjects have already fully met the IHS criteria for migraine at study entry. The algorithm used is based upon discussion with the Division and the aforementioned information faxed to Abbott by Ms. Chen. This algorithm used criteria C and D of the IHS codification for migraine with and without aura (IHS 1.1 and 1.2). Criteria A, B and E were acknowledged by the Agency to be inappropriate for classification of individual headaches. Central to the elimination of criterion B was the acknowledgement that a) prophylactic studies required allowance of abortive medications and b) that abortive treatment could and would alter aspects of migraines (e.g. they may diminish pain duration).

Compliance with the FDA provided algorithm was assessed in the two treatment groups of our 64 patient sample. In addition, patient characteristics were evaluated to assess the comparability of the treatment groups and to determine whether the sample was representative of the NDA intent-to-treat dataset (n=234). Four-week migraine headache rates considering all headaches coded as migraine, as well as only the headaches satisfying the FDA provided algorithm, were calculated and compared to the rates in the NDA intent-to-treat dataset.

Results indicated the following:

- 1047 of the 1176 headache events were coded by the sites as migraine headaches and had onset either during the Baseline or Experimental Phases of the study, and would therefore, have been considered in the original NDA intent-to-treat analyses. Of the 1047, the sites identified 110 as migraine headaches with aura and 937 as migraine headaches without aura.

- 92% (966/1047) of these migraine headaches were treated with an abortive medication.

- 673 (64%) of the 1047 migraine headaches were classified as migraine headaches per the FDA provided algorithm, including 340 (66%) of 518 migraine headaches in the placebo group and 333 (63%) of 529 migraine headaches in the Depakote ER group.

- The demographics and disease characteristics of the 64 patient sample were similar between the two treatment groups and similar to the characteristics of the NDA intent-to-treat dataset of the original NDA (see Attachments 1 and 2). The only exception is a treatment imbalance in the proportions of patients previously experiencing migraine headaches with aura or tension headaches in our sample. However, since migraines with aura represent only 11% of the sample and similar numbers of patients in each treatment group reported this migraine type, the sample results appear to be representative of the NDA intent-to-treat dataset.

- Results from the 64 subjects, which considered all headaches codes as migraine were compared to the NDA intent-to-treat results. The mean baseline and reduction-from-baseline four-week migraine headache rates considering all 1047 events coded as migraine headaches by the sites were similar to those of the intent-to-treat dataset (see Attachments 3 and 4).. Baseline rates were 4.0 and 4.3 for placebo and Depakote ER, respectively, versus 4.2 and 4.4 in the NDA intent-to-treat dataset; and reduction-from-baseline rates were 0.7 and 1.4 for placebo and Depakote ER, respectively, versus 0.6 and 1.2 in the NDA intent-to-treat dataset.

- Results from the 64 patients which considered only the headaches satisfying the FDA provided algorithm indicated a separation between treatment groups that was similar to that observed in the NDA intent-to-treat dataset. If the analysis was restricted to considering only the 673 migraine headaches satisfying the algorithm and it applied the 24-hour rule of combining migraine headaches not separated by a 24-hour headache-free interval only to those events, 7 of the 64 patients (2 placebo. 5 Depakote ER) would be lost from an analysis that required patients to have at least one of these events during the Baseline Phase to be included. The four-week migraine headache rates this analysis are summarized in Attachment 5 and described below.

	----------Placebo----------			----------Depakote ER----------		
	n	Mean (S.D.)	Median	n	Mean (S.D.)	Median
Baseline Phase	30	2.8 (1.4)	2.9	27	3.4 (2.0)	3.0
Experimental Phase Reduction	30	0.4 (1.6)	0.6	27	1.2 (1.8)	1.8

In summary. similar proportions of headaches reported by placebo- and Depakote ER-treated patients in the 64-patient sample satisfied the definition of migraine based on the FDA provided algorithm. The characteristics of this sample were representative of the NDA intent-to-treat dataset. An evaluation of headaches satisfying the algorithm indicated reductions in migraine headache rates were similar to those observed in the NDA intent-to-treat dataset.

Accordingly enclosed in four volumes are the CD-ROM and hard copies of the patient diaries for the 64 patients. Please note that the electronic version of the enclosed data is provided as a review tool. and that Abbott Laboratories does not consider the enclosed to represent a major amendment to our pending application.

Should you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Steven E. Townsend

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547
Fax: (847) 937-8002

SET/wet
Enclosures

Copy of this Cover Letter to:
Ms. Lana Chen, R.Ph., Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

ABBOTT

Chen

Pharmaceutical Products Division

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

January 28, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration, CDER
1451 Rockville Pike
Rockville, MD 20852

**RE: Depakote ER®
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168**

Four Month Periodic Safety Update

Dear Dr. Katz:

The purpose of this submission is to provide cross-reference to our January 28, 2000 submission (Serial No. 155) to IND ——, for safety information contained in the final clinical study report (—— for study —— entitled: ——", in order to meet obligations to periodically update a pending application with new safety information.

Reference is made to a January 21, 1999 telephone conversation with Ms. Lana Chen, of your staff, regarding: (1) submission of the final clinical study report for ——; (2) our request for a waiver contained in our original Depakote ER (migraine) NDA submission (NDA 21-168, Volume 22, page 015); and (3) the acceptability of providing a letter of cross-reference to IND —— to satisfy regulatory requirements for the four month periodic update of new safety information, "safety update reports" as required under 21 CFR 314.50 (5)(vi)(b). Based on our discussion, Ms. Chen recommended that we submit the information to IND —— as planned.

Clinical study —— was originally intended to be the basis for an NDA for —— We have reviewed the data from —— by the planned primary and secondary analysis. Unfortunately, the results of study —— do not provide sufficient proof of efficacy, therefore no NDA will be submitted at this time. Based on our review, no new information was learned from study —— that would

reasonably affect the statement of contraindication, warning, or precautions made to in our September 30, 1999 original NDA submission for Depakote ER Tablets. The Adverse Reactions section of draft labeling may be modified as appropriate to reflect events not listed in other patient populations currently noted in the draft labeling. In addition, there are no additional clinical studies ongoing or completed using Depakote ER Tablets.

Should you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Steven E. Townsend

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547
Fax: (847) 937-8002

SET/vh
Enclosures

Copy of this Cover Letter to:
Ms. Lana Chen, R.Ph., Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

Doris Bates, Ph.D., Project Manager
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

Jackie Ware, Pharm D., Project Manager
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

ABBOTT

Pharmaceutical Products Division

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

January 28, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Re: ——
IND —
Serial No. 155

INFORMATION AMENDMENT: Clinical Final Clinical Study Report ——
Request for a Meeting

Dear Dr. Katz:

Abbott Laboratories submits this amendment to the above Investigational New Drug Application under the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 312.31 and 21 CFR 312.47.

The purpose of this submission is to provide the final clinical study report ——, in fifteen (15) volumes, for study —— entitled: ——

——" and to request a meeting with the Division to discuss the results of this study and future development plans for Depakote ER Tablets, 500 mg.

Reference is made to an October 8, 1998 letter from Dr. Leber, formerly of the Division of Neruopharmacological Drug Products, and our subsequent teleconference of June 1, 1999 regarding the design of the study —— and the adequacy of a single study in support of a New Drug Application (NDA) for —— ——. During those communications it was established that a single positive adequate and well controlled study would be sufficient to support approval —— ——. We have reviewed the data from —— by the planned primary and secondary analysis. Unfortunately, the results of study —— do not provide sufficient proof of efficacy, therefore no NDA will be submitted at this time.

We have conducted a through review of the —— data including multiple post hoc analyses, evaluation of the study design, and consulted with advisors regarding factors that may have contributing to the study outcome. The summation of those activities is provided in the enclosed overview which contains some possible explanations for the results observed.

We are requesting that the Division grant a meeting to discuss the study results, possible study design issues that may have influenced the results, and the impact of these results on continued development of Depakote ER. In support of our request we commit that four weeks prior to the confirmed meeting date that we will provide a pre-meeting package consisting of a general development plan, questions for discussion, supportive/supplemental information, and list of attendees.

If you should have any questions or comments, please contact me at the number listed below. In the near future I will contact Dr. Doris Bates, of your staff, to initiate plans for the requested meeting.

Sincerely,

ABBOTT LABORATORIES

Steven E. Townsend

Steven E. Townsend, Associate Director
PPD Regulatory Affairs
D491, AP6B-1, (847) 938-9547
Fax: (847) 937-8002

SET/vch
Enclosures

Copy of this cover letter to:

Doris Bates, Ph.D., Project Manager
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

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

Lana Chen, R. Ph., Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

ABBOTT

Pharmaceutical Products Division

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

January 18, 2000

Armando Oliva, M.D.,
Medical Reviewer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration, CDER
1451 Rockville Pike
Rockville, MD 20852

RE: Depakote ER®
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 21-168

General Correspondence
Response to FDA Request for Information

Dear Dr. Oliva:

Reference is made to your telephone request of January 11, 2000 regarding clarification of the reference cited in our January 5, 2000 response (question number 2) to your December 27, 1999 facsimile. We have reviewed the citation and have determined that a error was made for the reference. The reference should have been Cephalalgia 8: (Suppl 7), 19-24, 1988 rather than the Cephalgia 8:(Suppl 7) 19-24, 1998 we indicated. We apologize for any inconvenience this discrepancy may have caused. For ease of your review we are enclosing a copy of the cited reference.

Should you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Steven E. Townsend
Associate Director, PPD Regulatory Affairs
(847) 938-9547
Fax: (847) 937-8002

SET/vh
Enclosures

Copy of this Cover Letter to:
Ms. Lana Chen, Regulatory Management Officer
Division of Neuropharmacological Drug Products
Woodmont II, HFD-120
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852