

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-168/S-004

ADMINISTRATIVE DOCUMENTS

Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-NOV-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1411365 FEI : 1411365
ABBOTT LABORATORIES
1401 14TH AND SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No: 1617 AADA: 018723

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-DEC-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1415939 FEI : 1415939

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 20-782 SUPPL #

Trade Name Depakote ER Tablets
Generic Name divalproex sodium extended release

Applicant Name Abbott Laboratories HFD- 120

Approval Date December 20, 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 / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type(SE1, SE2, etc.)?

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 / /

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 /_✓_/

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 /_✓_/

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 /_✓_/

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 /_✓_/

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 / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-723 Depakote Tablets

NDA # 19-680 Depakote Sprinkle Capsules

NDA #

2. Combination product. Not applicable.

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 / /

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 / / 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 /___/ 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 /___/

- (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 /___/

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 #

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 /___/

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 /___/
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 #__, Study #

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 # _____ YES /___/ ! 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 /___/

If yes, explain: _____

Jacqueline H. Ware, Pharm.D.
Regulatory Project Manager

December 20, 2002
Date

Russell Katz, M.D., Division Director

December 20, 2002
Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

**APPEARS THIS WAY
ON ORIGINAL**

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
12/20/02 02:27:09 PM

Russell Katz
1/3/03 09:48:54 AM

**APPEARS THIS WAY
ON ORIGINAL**

**Certification Requirement
For Approval of a Drug Product
Concerning Using Services of Debarred Persons**

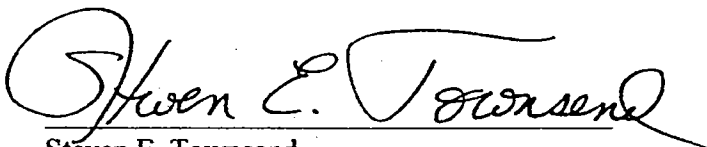
- DEBARMENT STATEMENT -

Any application for approval of a new drug product submitted on or after June 1, 1992, per FD&C Act Section 306 (k)(1), must include:

(1) A certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, subsection (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
Associate Director, Pharmaceutical Products Division
Regulatory Affairs
Abbott Laboratories
D. 491, Bldg. AP30-1NE
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

(847) 938-9547

(13.0) PATENT INFORMATION

Divalproex Sodium is covered by Patent Numbers 4988731 and 5212326. Patent Numbers 4988731 and 5212326 expire January 29, 2008. The Depakote ER 500 mg formulation is covered by Patent Number 4913906. Patent Number 4913906 expires April 3, 2007.

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-782 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 27, 2002 Action Date: December 20, 2002

HFD 120 Trade and generic names/dosage form: Depakote ER (divalproex sodium extended-release) Tablets

Applicant: Abbott Laboratories Therapeutic Class: 3S

Indication(s) previously approved: monotherapy and adjunctive therapy in complex partial seizures in adults and in simple and complex absence seizures in adults and dosing recommendations for converting adult patients from Depakote (divalproex delayed-release tablets) to Depakote ER tablets.

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: monotherapy and adjunctive therapy in complex partial seizures in adults and in simple and complex absence seizures in adults and dosing recommendations for converting adult patients from Depakote (divalproex delayed-release tablets) to Depakote ER tablets

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived: 0 to 1 month

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns

- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: 1 month - 16 years

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): not discussed with firm

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

**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
12/20/02 11:05:57 AM

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

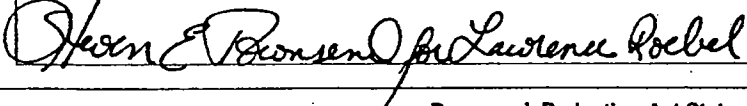
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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 Lawrence E Roebel, Ph.D.	TITLE Vice President, PPD Regulatory Affairs and Research Quality Assurance
FIRM/ORGANIZATION Abbott Laboratories	
SIGNATURE 	DATE 6-26-02

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 M00-232 Certification: Financial Interests and Arrangements of
Clinical Investigators**

Principal Investigator	Sub-Investigators / Coordinators
Williams, Laura A., MD, MPH (Investigator #14248, Site #1) Abbott Clinical Pharmacology Unit 1324 N. Sheridan Road Waukegan, IL 60085	

**APPEARS THIS WAY
ON ORIGINAL**

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

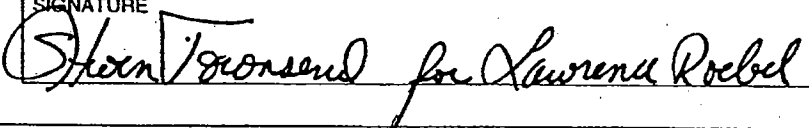
TO BE COMPLETED BY APPLICANT

The following information concerning See attached, who participated as a clinical investigator in the submitted study See attached, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Lawrence E Roebel, Ph.D.	TITLE Vice President, PPD Regulatory Affairs and Research Quality Assurance
FIRM/ORGANIZATION Abbott Laboratories	
SIGNATURE 	DATE 6-26-02

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 4 hours 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:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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Page(s) of trade

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REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D., Chair
HFD-530
9201 Corporate Blvd, Room N461

From: Paul Leber, M.D., Director,  7/24/97
Division of Neuropharmacological Drug Products, HFD-120

Date: July 22, 1997

Application Status (IND/NDA/ANDA): NDA 20-782

Proposed Proprietary Name: Depakote — Tablets

Trademark registration status/Countries registered(if known): status unknown

Company tradename: Abbott Laboratories

Other proprietary names by same firm for companion products:

Depakote Tablets (NDA 18-723)
Depakote Sprinkle Capsule (NDA 19-680)
Depakote-CP Tablet (NDA 19-794)
Depakene Capsules (NDA 18-081)
Depakene Syrup (NDA 18-082)

United States Adopted Name, dosage form, strength and dosing schedule:

Divalproex Sodium Controlled-Release Tablets; 500mg;
10-60mg/kg/day given QD or BID

Indication for use: Epilepsy (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; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures).

Comments from submitter (concerns, observations, etc.): None.

Attached for your reference is a copy of the firm's cover letter and form 356h, which accompanied the original NDA submission.

Meetings of the Committee are scheduled for the 4th Tuesday of each month. Please submit this form at least one week before the meeting. Responses will be as timely as possible. Rev. 2/97

NDA 20-782

Page 2

cc: NDA 20-782
HFD-120 Division file
HFD-120/Blum/Guzewska
HFD-120/Ware

file: 20782nam.c1

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: July 29, 1997 Time: 9:00am Location: WOC II Rm.4023

NDA# and Drug Name: NDA 20-782/ Depakote (divalproex sodium) Tablets
Indication: anticonvulsant

Type of Meeting: 45 day File/Refuse to File Meeting

Meeting Chair: Paul Leber, M.D.
Meeting Recorder: Jackie Ware, Pharm.D.

FDA Attendees:

Paul Leber, M.D., Director
Russell Katz, M.D., Deputy Director
Bob Rappaport, M.D., Clinical Reviewer
Ed Fisher, Ph.D., Pharmacology Reviewer
Ray Baweja, Ph.D., Biopharmaceutics Team Leader
Sayed Al-Habet, Ph.D., Biopharmaceutics Reviewer
Maryla Guzewska, Ph.D., Chemistry Reviewer
Martin Yau, Ph.D., Division of Scientific Investigations-Biopharmaceutics
Jackie Ware, Pharm.D., Project Manager

Meeting Objective(s):

To determine if NDA 20-782 is acceptable for filing.

Discussion Points and Decisions (agreements) reached:

Biopharmaceutics

- The application is considered to be fileable.

Chemistry

- The application is considered to be fileable.
- This application contains only information on the drug product. The drug substance information is cross-referenced to NDA-18-793.

Pharmacology

- The application is considered to be fileable.
- It was noted that in a March 22, 1996 submission to IND:47,713, the sponsor agreed to provide a report from Dr. Joan Lockard regarding data from her monkey study presented in *Epilepsia*, 18(2), 1997, pp 205-224. It does not appear that this report was received by the Agency. The CSO was requested to ask the sponsor what the status is on this report.

Clinical

- The application is considered to be fileable.

- This application does not contain any new efficacy data. It is a bioequivalency based NDA.

Inspections

- Dr. Baweja will advise Dr. Yau of DSIB of the specific studies for which an inspection request will be made.

Administrative

- The user fee due date for this application is June 17, 1998, given that it is considered to be a standard review.
- Technically, Dr. Temple has signatory authority on this NDA. However, it is possible that it will be delegated to Dr. Leber.
- Primary reviews for this NDA are due NO LATER than February 10, 1998. Dr. Leber emphasized to the team that reviews should be completed much earlier than this date, if possible.

Decision on fileability: Application is considered to be fileable.

Unresolved issues or issues requiring further discussion:

None.


Action Items

1. Notify firm of fileable status.
2. Inquire about the status of the report from Dr. Lockard.

Signature, minutes preparer: _____

Jackie Ware 8/7/97
Jackie Ware, Pharm.D.
Project Manager

Concurrence Chair (or designated signatory): _____


Paul Leber, M.D., Director
Division of Neuropharmacological
Drug Products

cc:

NDA Orig

HFD-120

HFD-120/Leber

/Katz/Rappaport/Blum/Guzewska/Fitzgerald/Fisher
Ware

HFD-860/Baweja/AI-Habet

file: 20782rtf.mm1

8/6/97

FSR 8/5/97

8/8/97

8/8/97

draft: 7/29/97

final: 8/7/97

MEETING MINUTES

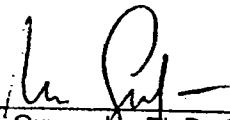
APPEARS THIS WAY
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MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA/IND #: NDA 20-782
DATE: 24-JUL-97
PRODUCT NAME: Depakote ~~Tablets~~
FIRM NAME: Abbott
SUBJECT: Drug Product Specifications
CONVERSATION WITH: Steven Townsend
TELEPHONE No.: (847) 938-9547

BACKGROUND: Release Specifications for Depakote ~~Tablets~~ are contained in Vol. 1.6, p. 11-22 (Document No. S41.07126). They are presented in a format Abbott uses for all of their products and are, therefore, unclear and difficult to define. The document includes tests that are not applicable to the finished product (e.g., limits for LoD of ~~_____~~), and there are several limits for content uniformity. Should the limits for tablet thickness and hardness be included in release specifications for the drug product?

I contacted Mr. Townsend and informed him that the release specifications for Depakote ~~Tablets~~ were unclear. I requested that they be presented in a different format (may be a table?), where both the tests to be performed and the appropriate limits be stated unambiguously.



M. Guzewska, Ph.D., Chemist

File: n20782.t01

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#: 20-782
PRODUCT NAME: Depakote ~~(Divalproex Sodium~~
~~)~~ Tablets
DATE: October 6, 1997
CONVERSATION WITH: Mr. Jim Steck, Director, Regulatory Affairs
FIRM NAME: Abbott Laboratories
SUBJECT: Request for the CMC section on electronic
discs
PHONE#: (847) 937-8002

4:43AM - 4:49AM: I called Mr. Steve Townsend, Project Manager, PPD Regulatory Affairs, at Abbott Laboratories but he wasn't available, so I talked with Mr. Jim Steck, Director, Regulatory Affairs. I requested an electronic copy of the CMC section of NDA 20-782 and Mr. Steck said he will look into it and call me back.


D. Klein, Ph.D., Review Chemist


cc:
NDA20-782
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/DKlein
HFD-120/ware
File: C:\hfd120\n20782\n20782TC#001

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#: 20-782
PRODUCT NAME: Depakote (Divalproex Sodium
 Tablets
DATE: October 7, 1997
CONVERSATION WITH: Mr. Steve Townsend, Project Manager, PPD
Regulatory Affairs
FIRM NAME: Abbott Laboratories
SUBJECT: Request for the CMC section on electronic
discs
PHONE#: (847) 938-9547

Approx. 9:00AM: Mr. Steve Townsend, Project Manager, PPD Regulatory Affairs, at Abbott Laboratories called and left a phonemail message. He said that only part of the CMC section for NDA 20-782 is available with some parts in Wordperfect and other parts in Microsoft Word.

10:16AM - 10:20AM: I called Mr. Steve Townsend, Project Manager, PPD Regulatory Affairs, at Abbott Laboratories but he wasn't available so I left a phonemail message. I said that if the CMC section was available this would make putting the CMC review together easier. However, since the CMC section isn't available then it isn't necessary to provide it electronically.


D. Klein, Ph.D., Review Chemist

cc:
NDA20-782
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/DKlein
HFD-120/JWare
File: C:\hfd120\n20782\n20782TC#002

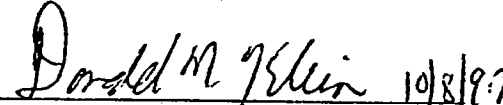
MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#: 20-782
PRODUCT NAME: Depakote (Divalproex Sodium _____
_____ Tablets
DATE: October 8, 1997
CONVERSATION WITH: Mr. Steve Townsend, Project Manager, PPD
Regulatory Affairs
FIRM NAME: Abbott Laboratories
SUBJECT: Request for the CMC section on electronic
discs
PHONE#: (847)938-9547

Approx. 8:30AM: Mr. Steve Townsend, Project Manager, PPD Regulatory Affairs, at Abbott Laboratories called and left a phonemail message. He wanted to discuss my request regarding the CMC section being available electronically.

11:36AM: I called Mr. Steve Townsend, Project Manager, PPD Regulatory Affairs, at Abbott Laboratories but he wasn't available so I left a phonemail message that I had returned his call.

11:55AM - 11:58AM: Mr. Steve Townsend called and he informed me that if there was a particular CMC section that I needed in electronic format then I should let him know and Abbott will attempt to provide it. I told Mr. Townsend that I would let him know which section I needed electronically.


D. Klein, Ph.D., Review Chemist

cc:
NDA20-782
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/DKlein
HFD-120/JWare
File: C:\hfd120\n20782\n20782TC#003

RECEIVED FEB 24 1998

FEB 20 1998

NDA#: 20-782

Submission Date:
July 25, 1997

Compound: Depakote (Divalproex Sodium)

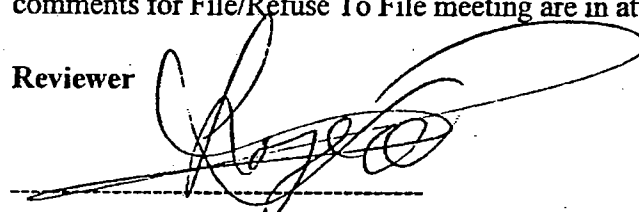
Sponsor: Abbott Laboratories Inc.

Reviewer: Sayed Al-Habet, Ph.D.

Background:

Abbott Laboratories, Inc. has submitted for review the above NDA. The reviewer's summary and comments for File/Refuse To File meeting are in attachment 1.

Reviewer



Sayed Al-Habet, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by Ray Baweja, Ph.D.

R. Baweja 2/20/98

cc: IND # 20-782, HFD-120, HFD-860 (Al-Habet, Baweja, Malinowski), Drug file (Barbara Murphy, Central Document Room).

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-168/S-004

CORRESPONDENCE



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500
June 16, 1997

Food and Drug Administration
San Juan District Office
466 Fernandez Juncos Ave
San Juan, Puerto Rico 00901-3223

Re: Depakote —
NDA No. 20-782

**ORIGINAL NEW DRUG APPLICATION:
Field Copy of Chemistry, Manufacturing,
and Controls NDA Technical Section**

Dear Sir or Madam:

Abbott Laboratories submits herewith a copy of to the chemistry, manufacturing, and controls (CMC) technical section for the above-referenced NDA, in accordance with 21 CFR 314.70. In addition, a copy of the application form (356h) for this NDA is included, in compliance with 21 CFR 314.50. The certification that the field copy of the CMC section is a true copy of the technical section is contained in the archival and technical section of this submission. This submission is eleven volumes.

Data contained within this supplement will be reviewed by the Division of Neuropharmacological Drug Products.

Should you have any questions or comments, please contact me at the number listed below.

Sincerely,

ABBOTT LABORATORIES

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



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

June 16, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

Re: Depakote
(Divalproex Sodium)
Tablets
NDA No. 20-782

ORIGINAL NEW DRUG APPLICATION

Dear Sir or Madam:

The applicant, Abbott Laboratories, submits herewith an original new drug application (NDA) for Depakote® (Divalproex Sodium) Tablets in accordance with the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50. This application contains information in accordance with our June 7, 1996, submission to Investigational New Drug (IND) application No. 47,714 (Divalproex Sodium) and as agreed to in a July 11, 1996, letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products.

The pre-assigned NDA number for this application is NDA 20-782. The User Fee I.D. number for this application is 3093. The appropriate user fee payment has been transmitted and a copy of the user fee form FDA 3397 and the transmittal letter are enclosed.

Reference is made to a May 15, 1996, teleconference between representatives of the Division of Neuropharmacological Drug Products and representatives of Abbott Laboratories. Abbott Laboratories was advised that the Agency had adopted a new policy regarding the requirements for a formulation for marketed antiepilepsy products with well-established efficacy and safety profiles. This new position required the sponsor of such a CR formula to show in biostudies that the fluctuations in drug concentration are decreased with the dosage form versus the immediate release product, and that total systemic exposure is equivalent.

Depakote — (Divalproex Sodium) Tablets

NDA No. 20-782

Original New Drug Application

June 16, 1997

Page 2

This NDA provides data for a Depakote® — Tablet 500 mg Valproic Acid Equivalent formulation which will allow a once-daily administration regimen with less fluctuation in plasma concentrations than the commercial reference formulation administered in divided doses in patients taking Depakote with or without enzyme inducing antiepilepsy drug. Depakote — Tablets are 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. Depakote — tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

This submission consists of 32 volumes. Archival and Technical Review copies, are provided for Section 2 (Summary), Section 3 (Chemistry/Manufacturing/Controls), Section 4 (Samples/Labels/Methods Validation), Section 6 (Human Pharmacokinetics and Bioavailability), and Sections 8 & 9 (Clinical Data/Safety Update Report). Only Archival copies are provided for Section 12 (Case Report Forms). Volume 1, which contains this letter, the 356h form, NDA index, NDA Summary (including annotated draft labeling), patent information, and Certification of the Field Copy and Debarment Statement (section 2.10) has been included for each technical section.

In addition, a complete copy of the CMC section, 356h form, NDA summary and the certification of field copy are being sent to our FDA District Office, as required under 21 CFR 314.50(k)(2). We have also sent a copy of this CMC section to our San Juan District Office in whose jurisdiction our Puerto Rico drug product facility is located.

Section 3 (Chemistry/Manufacturing/Controls) cross references the drug substance information to our approved NDA 18-723 for Depakote Delayed Release Tablets. Stability data for Depakote — Tablets will be provided as proposed in our December 19, 1995, submission (Serial No. 003) (i.e. submission of 12 month real time and 6 months accelerated data in our original application with a commitment to amend the application to provide 18 month data within 9 months of the submission to support our proposed expiration dating of twenty four (24) months) and as discussed with Stanley Blum, Ph.D., during a March 20, 1996, telephone conversation.

Depakote — (Divalproex Sodium) — Tablets
NDA No. 20-782
Original New Drug Application
June 16, 1997
Page 3

In accordance with our above referenced July 11, 1996, communication Section 8 (Clinical) contains a repeat of Section 6 (Human Pharmacokinetics and Bioavailability section) and Final Clinical Summaries which include all safety data for each individual study. Section 8 does not contain an Integrated Summary of Efficacy (ISE), or an Integrated Summary of Safety (ISS). Adverse events are discussed in the individual final clinical reports provided in the Reference portion of Section 8.0 of this submission (Volumes 19-31).

Please note in Section 9 (Safety Update Report) that we have requested a waiver in accordance with 21 CFR 314.90 for the four month periodic update of new safety information "safety update reports" required under 21 CFR 314.50 (5)(vi)(b) because all clinical studies of Depakote — Tablets conducted by Abbott Laboratories have been completed and the data is provided in this NDA. No additional clinical studies are planned.

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

Sincerely,



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

SET:kdh
Enclosures

Copy of this Cover Letter to:
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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-782

Abbott Laboratories
Pharmaceutical Products Division
Attention: Steven E. Townsend
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

JUN 23 1997

Dear Mr. Townsend:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Depakote — (divalproex sodium —————) Tablets

Therapeutic Classification: Standard

Date of Application: June 16, 1997

Date of Receipt: June 17, 1997

Our Reference Number: 20-782

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 15, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Jacqueline H. Ware

(For) John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500
June 30, 1997

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

Re: Depakote —
(Divalproex Sodium
Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE
Electronic Version of Draft Labeling

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith the enclosed information to our new drug application (NDA No. 20-782) for Depakote® — (Divalproex Sodium ~~Tablets~~) ~~Tablets~~ in accordance with the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

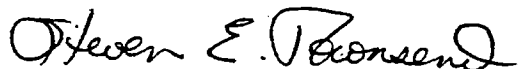
The purpose of this submission is to provide an electronic version of the proposed draft labeling included in our original NDA submission provided on June 16, 1997, as requested by Dr. Jackie Ware, of your staff, during a June 20, 1997, telephone conversation with me. The enclosed diskette contains two files in WordPerfect for Windows 5.2: These files contain the shaded text version of the draft labeling (file:dn299v3) included in our original submission and a non-shaded version (file:dn299v3.fin). A printed copy of each file has been included in this submission as reference.

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

Depakote
NDA No. 20-782
June 30, 1997
Page 2

Sincerely,

ABBOTT LABORATORIES



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

SET:kdh
Enclosures

Copy of this Submission to:
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
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157

June 26, 2002

RECEIVED ORIGINAL
JUN 27 2002
HFD-120/CDER

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

ORIGINAL AMENDMENT

RE: Depakote® ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 20-782

Complete Response to Action Letter

MTB
1

Dear Dr. Katz,

The applicant, Abbott Laboratories, submits herewith a complete response to the June 17, 1998 action letter for Depakote® ER (Divalproex Sodium Extended-Release) Tablets, in accordance with our June 25, 1998 response to the action letter and the provisions of Section 505 (i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314. This submission contains information regarding the original action letter and provides cross-reference to NDA 21-168 (Depakote ER, Migraine) approved August 4, 2000, and NDA 21-168/S-001 approved May 31, 2002.

Reference is made to our October 12, 2000 and March 21, 2001 submissions to IND 47,714 (Serial No. 023 and 024, respectively), and our January 3, 2001 and May 3, 2001 meetings with the Division of Neuropharmacological Drug Products. These communications established the basis for the data necessary to support approval of Depakote ER for the treatment of epilepsy in accordance with currently approved valproate products. This included two additional bioequivalence studies (M00-232 and M01-274) using an 8-20% higher dose of Depakote ER vs Depakote Delayed-Release Tablets. These two studies were conducted in healthy subjects and in epilepsy patients on enzyme inducing anti-epilepsy drugs, respectively. Results of these studies demonstrate that when Depakote ER is given in doses 8 to 20% higher than the total daily dose of Depakote Delayed-Release Tablets, the two formulations are bioequivalent.

Depakote ER
(Divalproex Sodium Extended-Release Tablets)
NDA 20-782
June 26, 2002
Page 2

Accordingly, this submission contains draft labeling, an overview and summary of the bioavailability of Depakote ER (Report R&D/02/323), and final clinical study reports for study M00-232 entitled; "Comparison of the Bioavailability of Depakote Extended-Release Formulation (1000 and 1500 mg Total Daily Dose) Relative to Depakote Delayed-Release Formulation (875 and 1250 mg Total Daily Dose) in Healthy Volunteers" (Clinical Study Report No. R&D/01/028) and study M01-274 entitled; "Comparison of the Bioavailability of a Depakote Extended-Release Formulation Relative to the Depakote Delayed-Release Tablet Formulation in Adult Patients with Epilepsy on the Depakote Delayed-Release Tablet Formulation and an Enzyme-Inducing Antiepileptic Drug" (Clinical Study Report No. R&D/02/242).

As part of the complete response we have included copies of responses previously provided to Biopharmaceutics and Chemistry, Manufacturing, and Controls (CMC) comments (Attachment A and B) contained in the June 17, 1998 action letter. These responses have been previously reviewed by the Agency to support the August 4, 2000 approval of NDA 21-168 (Depakote ER, Migraine). Please note that the CMC response was also provided in our October 7, 1998 submission to NDA 20-782. In addition, we are cross-referencing NDA 21-168/S-001 approved May 31, 2002 for our Depakote ER 250 mg formulation in accordance with the May 3, 2001 meeting referenced above.

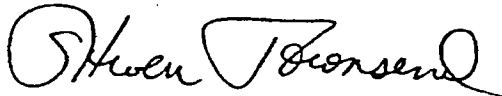
As indicated in the May 3, 2001 meeting minutes provided by Melina Fanari, R.Ph., of your staff, Abbott Laboratories requests a deferral from pediatric use information for this application in accordance with 21 CFR 314.55(b). We are requesting this deferral pending the outcome of our Proposed Pediatric Study Request submitted on June 22, 2001 to NDA 21-168 (Depakote ER, Migraine).

This submission consists of 11 volumes. Volume 1 contains this letter, Form 356h, updated patent information, debarment, and financial information regarding studies M00-232 and M01-274 referenced above.

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

Sincerely,

ABBOTT LABORATORIES



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

SET

Depakote ER
(Divalproex Sodium Extended-Release Tablets)
NDA 20-782
June 26, 2002
Page 3

Copy of submission to:

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

**APPEARS THIS WAY
ON ORIGINAL**

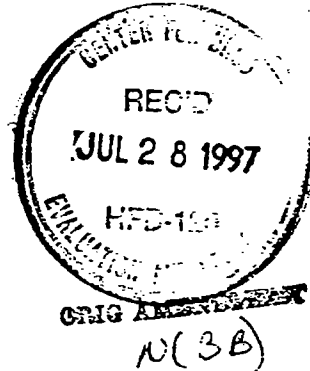


ABBOTT

ORIGINAL

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500
July 25, 1997



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

Re: Depakote
(Divalproex Sodium)
Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith the enclosed information to our new drug application (NDA No. 20-782) for Depakote® (Divalproex Sodium) Tablets in accordance with the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

Reference is made to our June 7, 1996 submission to IND No. 47,714 (Divalproex Sodium) Tablets) and a September 11, 1996 facsimile from Dr. Jackie Ware, of your staff. In that facsimile a request from the Division of Biopharmaceutics was made to provide NONMEM and ADAPT II files and raw data files that were used for modeling of the *in vitro/in vivo* data (Study M95-414) included in our New Drug Application submitted on June 16, 1997. Reference is also made to a July 21, 1997 telephone conversation between Sayed Al-Habet, Ph.D., and myself regarding arrangements for submitting the requested electronic data.

Accordingly, the purpose of this submission is to provide the requested electronic data. The data consists of seven files on one data disk. The following table provides a list of the filenames with a description of what is contained in each file.

Depakote
NDA No. 20-782
July 25, 1997
Page 2

File Name	Contents
Read.Me	Text file with description of data files
iviv.dat	The data set for the NONMEM analysis in Study M95-414 (Ascii file). Column 1 is the subject number; Column 2 is the period number; Column 3 is the regimen; Column 4 is the time after last dose; Column 5 is the percent absorbed in vivo; Column 6 is the percent dissolved in vitro; Column 7 is the PH value; Column 8 is the rpm value; Column 9 is the mM value.
iviva.nmt	The NONMEM code for the full model in Study M95-414 (Ascii file).
ivivb.nmt	The NONMEM code for the reduced model in Study M95-414 (Ascii File).
WAGNER_n.dat	The data set for all individual concentrations and percent absorbed in Study M95-414 (Ascii file). Column 1 is the regimen; Column 2 is the subject number; Column 3 is the time after last dose; Column 4 is VPA plasma concentration; Column 5 is the percent absorbed in vivo based on Wagner-Nelson method.
finalivivc.for	The ADAPT II code file (text formatted).
M95414.dat	The data file for the ADAPT II code (text formatted).

In addition, we are providing a printed copy of each of the six data file as reference.

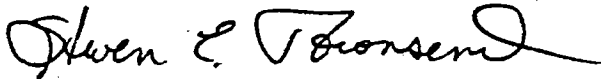
The enclosed data is an electronic duplication of data provided in our original New Drug Application (NDA No. 20-782). Therefore, Abbott Laboratories does not consider this submission to be a major amendment to this application.

Depakote
NDA No. 20-782
July 25, 1997
Page 3

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

Sincerely,

ABBOTT LABORATORIES



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

SET:kdh
Enclosures

Copy of this Submission to:
Sayed Al-Habet, Ph.D., Biopharmaceutics Reviewer
Division of Biopharmaceutics
Woodmont II, HFD-426
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

Copy of the Cover Letter to:
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 60064-3500
October 23, 1997

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

Re: Depakote ~~_____~~
(Divalproex Sodium
~~_____~~), Tablets
NDA No. 20-782

**AMENDMENT TO A
PENDING APPLICATION:
Updated Stability Data**

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith an amendment to our pending New Drug Application (NDA) No. 20-782 for Depakote® ~~_____~~ (Divalproex Sodium ~~_____~~) ~~_____~~ Tablets submitted June 16, 1997 in accordance with the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

The purpose of this submission is to provide updated stability data for Depakote ~~_____~~ tablets contained in Volume 8 (pages 015 - 320) of our original submission. The enclosed provides 15 and 18 month data for all lots except bottles of six tablets packaged at our Abbott Park facility (Stability Studies 121-00E-029-4, 121-00E-027-8, and 121-00E-028-6) which are updated with 12 month data versus the 9 month data originally submitted.

Reference is made to a September 24, 1997 telephone conversation between myself and Dr. Jackie Ware, of your staff, who indicated that the Reviewing Chemist, Dr. Donald Klein, had agreed with our request to provided stability data for the above-referenced drug product in accordance our original June 16, 1997 submission and our March 20, 1996 telephone conversation with Stanley Blum, Ph.D., formerly of your staff. Because of the above-referenced communications Abbott Laboratories does not consider this submission to be a major amendment to the application.

Depakote ←
NDA No. 20-782
October 23, 1997
Page 2

The enclosed updated stability tables provide data for Potency, Physical Inspection, Moisture, Degradation Products, and Dissolution. This submission also contains Report R&D/97/605 entitled; "Divalproex Sodium ← Tablets 500 mg Stability: Update of Kinetic/Statistical Analysis of Potency Data", which replaces R&D/97/266 provided in our original submission (Volume 8, page 352). The data in this submission continues to support our proposed expiration dating of twenty-four (24) months for Depakote — Tablets in all packaging configurations.

In addition, a copy of this submission and a certification of a field copy are being sent to our FDA District Offices (Chicago and San Juan) as required under 21 CFR 314.50(k)(3) and 21 CFR 314.60(c).

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

Sincerely,

ABBOTT LABORATORIES



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

SET:kdh
Enclosures

Copy of the Cover Letter to:
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 60064-3500
January 29, 1998

Donald Klein, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

Re: Depakote
(Divalproex Sodium)
Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE

Dear Dr. Klein:

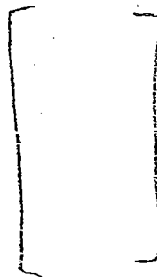
The sponsor, Abbott Laboratories, submits the enclosed in support of our pending New Drug Application (NDA) 20-782 for Depakote® (Divalproex Sodium) Tablets in accordance with provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.

The purpose of this submission is to provide samples of container closure material (bottles, caps, desiccant, and blister material) as you requested during our January 23, 1998 telephone conversations. Enclosed you will find five plastic bags which contain bottles, caps, and desiccants, and three cards which contain representative samples of blister material. All items have been labeled with their commodity name, number, and location within the application for the respective specifications. Please note that we have only sent one example of the Film material (Commodity Number _____). Commodity Number _____, and Commodity Number _____ are the same material but differ in width (186 mm vs. 8 inches).

Accordingly enclosed are the samples of the following container closure systems for Depakote
Tablets:

<u>Description</u>	<u>Specification Number</u>
Bottle, Plastic, 1 Ounce	[]
Bottle, Plastic, 4 Ounce	
Bottle, Plastic, 5 Ounce	
Bottle, Plastic, 32 Ounce	
Cap, _____, 24 MM	[]
Cap, _____, 38 MM	
Cap, _____	

Specification Number



Depakote
NDA No. 20-782
January 29, 1998
Page 2

Desiccant, Canister, _____ 1 Gram
Desiccant, Canister, _____ 2 Gram

Foil, Roll, Unprinted _____
Foil, Roll, Unprinted Push Thru _____
Film Unprinted Roll _____
Film Unprinted Roll _____

Bottle, Plastic, 1 Ounce**
Bottle, Plastic, 4 Ounce**
Bottle, Plastic, 5 Ounce**

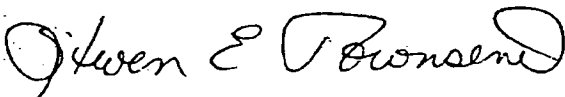
Cap, _____
Cap, _____

* Commodity Number _____ and Commodity Number _____ are the same material but differ in width (186 mm vs. 8 inches).
** _____ Packaging

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

Sincerely,

ABBOTT LABORATORIES



Steven E. Townsend
Product Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of this Cover Letter to:
Jackie Ware, Pharm. D., Project Manager
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

**ABBOTT****Pharmaceutical Products Division**

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

February 5, 1998

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

Re: Depakote
(Divalproex Sodium
Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits the enclosed in support of our pending New Drug Application (NDA) 20-782 for Depakote® (Divalproex Sodium) Tablets in accordance with provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.

The purpose of this submission is to provide updated letters of authorization for Drug Master File (DMF) originally provided in our June 16, 1997 submission (Volume 5, Page 228). Reference is made to January 26, 1998 and February 2, 1998 telephone conversations between Dr. Donald Klein, of your staff, and myself regarding DMF and a request for clarification of the specific referenced within the DMF letter of authorization for peelable and push-thru foil rolls used in blister packaging for Depakote tablets (Commodity No. (peelable) and Commodity No. (push-thru)). As a result of those conversations has provided two new letters of authorization to DMF for (Commodity No. , and (Commodity No.)



Depakote / —
NDA No. 20-782
February 5, 1998
Page 2

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

Sincerely,

ABBOTT LABORATORIES

Steven E. Townsend
Product Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of this submission to:
Donald Klein, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

Copy of this cover letter 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

**ABBOTT****Pharmaceutical Products Division**

Abbott Laboratories
 100 Abbott Park Road
 D-491, AP6B-1SW
 Abbott Park, Illinois 60064-3500

February 5, 1998

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

Re: Depakote
 (Divalproex Sodium
 Tablets
 NDA No. 20-782

GENERAL CORRESPONDENCE

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits the enclosed in support of our pending New Drug Application (NDA) 20-782 for Depakote® (Divalproex Sodium Tablets) in accordance with provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.

The purpose of this submission is to provide updated letters of authorization for Drug Master File (DMF) originally provided in our June 16, 1997 submission (Volume 5, Page 228). Reference is made to January 26, 1998 and February 2, 1998 telephone conversations between Dr. Donald Klein, of your staff, and myself regarding DMF and a request for clarification of the specific " " referenced within the DMF letter of authorization for peelable and push-thru foil rolls used in blister packaging for Depakote tablets (Commodity No. (peelable) and Commodity No. (push-thru)). As a result of those conversations has provided two new letters of authorization to DMF for (Commodity No.), and (Commodity No.).



Depakote / —
NDA No. 20-782
February 5, 1998
Page 2

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

Sincerely,

ABBOTT LABORATORIES

Steven E. Townsend
Product Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of this submission to:

Donald Klein, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

Copy of this cover letter 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



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

February 9, 1998

Donald Klein, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

Re: Depakote —
(Divalproex Sodium
—————) Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE

Dear Dr. Klein:

The sponsor, Abbott Laboratories, submits the enclosed in support of our pending New Drug Application (NDA) 20-782 for Depakote® — (Divalproex Sodium ————) Tablets in accordance with provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.

Reference is made to our telephone conversations on February 5 and 9, 1998 regarding the use/justification of the desiccants (Commodity No. ———) and Commodity No. ———, in the container/closure systems for Depakote — Tablets (NDA 20-782). As we discussed this morning the NDA stability lots provided in our application were conducted using the above referenced desiccants and are intended to be part of our to-be-marketed bottle packaging configuration. The reason desiccant cans were used originally was based on scientific judgement and the knowledge of the formulation. Essentially the desiccants were added to prevent the uptake of water vapor into the tablet core. All of the tablet's ingredients are known to be hydrophilic. In particular, the ———, hydroxypropyl methylcellulose (————), which is present as ———, of the tablet core, ———. The tablet ———.

Depakote Sprinkle Capsules (NDA 19-680) are packaged with desiccant for the same reason (to prevent the uptake of moisture by the formulation). Depakote Delayed Release Tablets (NDA 18-723) however, are not packaged with a desiccant. In this case the tablet's ———.

Depakote —
NDA No. 20-782
February 9, 1998
Page 2

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

Sincerely,

ABBOTT LABORATORIES



Steven E. Townsend
Product Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
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Jackie Ware, Pharm. D., Project Manager
Division of Neuropharmacological Drug Products
HFD-120, Woodmont Office Complex 2
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Rockville, MD 20852



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
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Abbott Park, Illinois 60064-3500

April 13, 1998

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

Re: Depakote —
(Divalproex Sodium
Tablets
NDA No. 20-782

GENERAL CORRESPONDENCE
Updated Draft Labeling

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith updated draft labeling for our new drug application (NDA No. 20-782) for Depakote® (Divalproex Sodium ~~Tablets~~) Tablets in accordance with the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

Reference is made to telephone conversations on March 2, 16, 19, and 25, and April 2 and 10 between Dr. Jackie Ware, of your staff, and myself regarding the proposed trademark and generic name for Depakote ~~and~~ and minor changes to the draft labeling. Based on those conversations we are requesting that the trademark and generic name for NDA 20-782 be changed from "Depakote ~~(Divalproex Sodium ~~Tablets~~) Tablets~~" to "Depakote ER (Divalproex Sodium Extended-Release Tablets)".

In addition, enclosed is an updated version of the draft labeling provided with our June 16, 1997 original submission to NDA 20-782 which incorporates the new trademark and generic names as well as changes to the text to bring the information into alignment with other approved Abbott Depakene/Depakote product labeling (i.e. "There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established." in the ADVERSE REACTIONS section as provided in our November 6, 1997 response to your request of September 8, 1997 to NDA 18-723), and changes as a result of the FDA Modernization and Accountability Act of 1997 (i.e. deletion of the "Caution-- Federal (U.S.A.) Law prohibits dispensing without a prescription" from the draft labeling). The statement "Rx only" will appear on package labels.

Depakote
NDA No. 20-782
April 13, 1998
Page 2

The enclosed printed copy of draft labeling has the text unique to Depakote ER shaded in the same manner as provided in volume 1 of our original application. No other changes have been made to the text (except as noted above). The electronic version provided is in WP 6.1. Please note that the legend in Figure 1 of the draft labeling still contains the Depakote naming convention because this figure exists only as a picture file within the current electronic version of the draft labeling and will be updated in the final printed labeling accordingly.

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

Sincerely,

ABBOTT LABORATORIES



Steven E. Townsend
Project Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of the Submission to:
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 60064-3500

May 21, 1998

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

**Re: Depakote ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 20-782**

Response to FDA Request for Information

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith a response to an FDA request for information for our new drug application (NDA No. 20-782) for Depakote® ER (Divalproex Sodium Extended-Release) Tablets in accordance with the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

Reference is made to telephone conversations on May 13 and 18, 1998 between yourself and members of your staff, and Abbott representatives regarding data from Study M95-376 entitled, "Evaluation of the Absorption Characteristics of Two Oral Dosage Forms of Divalproex Sodium Under Multiple-Dose Conditions" that was included in our original NDA submission (June 16, 1997). During those teleconferences concern was raised about the suboptimal performance of the formulation under fasting conditions in Study M95-376, based on low C_{min} and AUCs for two subjects (Subject No. 5 and No. 10) relative to the reference (Depakote Delayed-Release Tablets). The question was advanced as to whether this performance indicates an intrinsic fault with the formulation and whether the finding under fasting conditions applies to nonfasting conditions. Therefore, the purpose of this submission is to provide our evaluation of the data based on review of the individual subject data, product performance data, and data obtained from other studies/sources.

Depakote ER
NDA No. 20-782
May 21, 1998
Page 2

Depakote ER tablets were engineered taking into account the physicochemical and pharmacokinetic characteristics of valproate, as well as the normal physiology and dynamics of the gastrointestinal tract. *In vitro* testing has shown that the formulation is extremely consistent, with approximately 100% delivery of drug by 12 hours, and complete release thereafter. In our original NDA submission, we evaluated the multiple-dosing bioavailability (AUC) and fluctuation (DFL) of the formulation relative to the reference given more-frequently in accordance the Division's pre-established policy for approval of a controlled-release version of currently marketed anti-epileptic medications. The formulation satisfied these criteria, although performance was more variable under fasting conditions. Based on our recent review of the data, we concur with the reviewing Division that the two subjects in M97-376 under fasting conditions had low C_{min} and we acknowledge the concern for a small fraction of the epileptic population which may be affected by lower plasma concentrations under fasting conditions. However, in the nonfasting state, Depakote ER is bioequivalent to the reference and meets the Division's intended requirements. It is our opinion that these results are consistent with the *in vitro* characteristics of the formulation, the known dependence of gastric residence for solid dosage forms on unit size and food content, and the population variability in total gastrointestinal transit times, and we would propose that this issue can be addressed with appropriate labeling and specific recommendations for the use of Depakote ER tablets.

Therefore, we are proposing to modify the Depakote ER labeling to incorporate language requiring that the product be taken with food and caution physicians that significantly lower absorption may occur in some individuals or in cases where fast transit (e.g. diarrhea) may exist. This could result in a small minority of patients in whom AUC and C_{min} may be lower than that of the marketed Depakote Tablets. In addition, therefore we would include in the labeling a Precaution statement to indicate that when switching from valproate products to Depakote ER, or when seizure activity is altered, plasma concentration monitoring may be appropriate to guide dosage adjustment. It should be noted that our original NDA submission contained draft labeling (DOSAGE AND ADMINISTRATION) which stated, "As with other valproate products, doses of Depakote ER should be individualized and titration may be necessary. In selected patients, twice-a-day regimen may be chosen. If a twice-a-day regimen is preferred, and the dose is unequal, the larger dose should be given in the evening (e.g., for 1500 mg/day, give 500 mg in the morning and 1000 mg in the evening). If a patient requires closer titration than that available with Depakote ER doses in increments of 500 mg, Depakote tablets or Depakote Sprinkle Capsules should be used."

In support of our application we have enclosed an overview of the existing data which provides a more detailed explanation of subject data, product performance data, arguments for the administration of the product with food, and proposed text to be incorporated into draft labeling referenced in the above text.

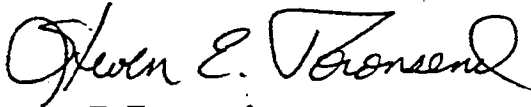
Depakote ER
NDA No. 20-782
May 21, 1998
Page 3

Please note that Abbott Laboratories does not consider the enclosed information to constitute a major amendment to the application.

Should you have any questions or comments regarding this submission, please contact me at the number listed below. In addition, we would appreciate receiving feedback from the Division regarding this submission prior to the issuing of an action letter.

Sincerely,

ABBOTT LABORATORIES



Steven E. Townsend
Project Manager, PPD Regulatory Affairs
Tel: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of the Submission to:

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

Russel Katz, M.D., Deputy Director
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 60064-3500

May 28, 1998

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

**Re: Depakote ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 20-782**

Response to FDA Request for Information

Dear Dr. Leber:

The sponsor, Abbott Laboratories, submits herewith a response to an FDA request for information for our new drug application (NDA No. 20-782) for Depakote® ER (Divalproex Sodium Extended-Release) Tablets in accordance with the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

Reference is made to telephone conversations on May 28, 1998 between Rae Yuan, Ph.D. and Chandra Sahajwalla, Ph.D., of your staff, and James Steck, of Abbott Laboratories regarding NDA 20-782 (Depakote ER) and data from Study F93-236 entitled, "Evaluation of the Effect of Food on the Absorption Characteristics of Divalproex Sodium Tablets" that was included in our NDA 18-723 (Supp S-017) submission for the prophylaxis of migraine headache, submitted on June 30, 1994 (Vol 5C of 163). Dr. Yuan requested that we provide the AUC, C_{max} , and C_{min} data for subjects included in study F93-236 and the statistical analysis of the original data.

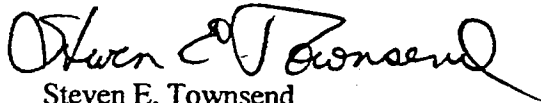
The purpose of this submission is to provide a complete copy of the original report (Study F93-236) to aid in Dr. Yuan's review of the data previously faxed (Abstract pages v - vii, page 10 of the text, and tables 7, 8, and 9). Study F93-236 provides a comparison of C_{max} , C_{min} , and AUC for Depakote Delayed Release Tablets administered q12h under fasting and non-fasting conditions.

Depakote ER
NDA No. 20-782
May 28, 1998
Page 2

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

Sincerely,

ABBOTT LABORATORIES



Steven E. Townsend
Project Manager, PPD Regulatory Affairs
Phone: (847) 938-9547
Fax: (847) 937-8002

SET:kdh
Enclosures

Copy of the Submission to:

Rae Yuan, Ph.D.
Primary Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Woodmont II, HFD-850
Food and Drug Administration/CDER
1451 Rockville Pike
Rockville, MD 20852

Copy of the Cover Letter to:

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Ware

Food and Drug Administration
Rockville MD 20857

NDA 20-782

Abbott Laboratories
Abbott Pharmaceutical Products Division
Attention: Steven E. Townsend
Project Manager, PPD Regulatory Affairs
100 Abbott Park Road, D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

JUN 17 1998

Dear Mr. Townsend:

Please refer to your new drug application dated June 16, 1997, received June 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote ER (divalproex sodium extended-release tablets) 500mg.

We acknowledge receipt of your additional correspondence and amendments dated:

June 30, 1997	January 29, 1997	April 13, 1998
July 25, 1997	February 5, 1998	May 21, 1998
October 13, 1997	February 9, 1998	May 28, 1998
October 23, 1997		

The User Fee goal date for this application is June 17, 1998.

This original new drug application provides for an extended-release formulation of divalproex sodium which will allow for a once-daily dosing regimen as compared to an already marketed preparation of divalproex sodium (Depakote Delayed-Release Tablets).

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). Our reasons are as follows.

You have performed two definitive bioequivalence studies that compare the pharmacokinetics of the Depakote ER and Depakote Delayed-Release (DR) preparations. Study M95-376 was performed in healthy volunteers not receiving concomitant antiepileptic drugs (AEDs) and evaluated the pharmacokinetics of the ER formulation in the fed and fasted state compared to the DR formulation given in the fasted state. Study M95-401 was performed in patients with epilepsy who were receiving a concomitant AED; all treatments were given in the fed state.

In Study M95-401, the ER and DR preparations of divalproex sodium were shown to fall within 80 - 125% range of 90% confidence interval (CI).

In Study M95-376, the AUCs of the ER and DR preparations were equivalent. The C_{max} of the ER in the fasted state was low compared to that of the DR preparation, and failed standard equivalence criteria. This lower C_{max} is not a problem, because, as you know, the Division has agreed that valproate products designed to be given less frequently than available products can be considered equivalent to those marketed products if the AUCs are the same, but fluctuations in plasma levels are less (lower C_{max} and greater C_{min}).

However, the C_{min} of the ER formulation in the fasted state is also lower than the C_{min} of the DR marketed preparation, and does not fall within 80 - 125% range of 90% CI. Inspection of the individual patient data reveals two patients, Patients 5 and 10, whose Day 6 plasma concentration-time curves for the fasted ER treatment regimen demonstrate that plasma valproate levels are consistently lower throughout the day than the C_{min} for the DR tablet. This pattern of data suggests unacceptable product performance. (It is important to note that Depakote is approved as monotherapy for various seizure types; because of this, we believe the study in healthy subjects not receiving concomitant AEDs is an appropriate test system in which to evaluate the performance of the ER product).

For these reasons, we cannot conclude that the ER product has been shown to be equivalent to the marketed Depakote tablet.

We have reviewed your amendment dated May 21, 1998 which is intended to address this concern. In that amendment, you assert that the product might not perform adequately in a "... small subset of patients...", related to the rapid gastric emptying time associated with the fasted state. For this reason, you urge us to approve the product with labeling that advises that the product should be given with food.

Assuming that the poor performance of the product was, in fact, related to gastric emptying time (a point which you have not proved), we still find that your proposed solution is inadequate to insure acceptable product performance.

First, we disagree that the demonstration of an acceptable plasma time concentration profile in the fed stated adequately insures that the product will perform adequately in the wider population of "fed" patients. Our concern arises from the fact that the product performed poorly in 2/14 fasted patients, an incidence that we cannot agree constitutes a small subset. Given this rate of failure, we are not convinced that the demonstration of reasonable performance in only 14 fed patients (the same patients, of course) is sufficiently robust to erase the concern raised by the poor performance in 2 of these subjects under different conditions.

Further, you assert that a direct comparison of the performance of the ER product under fed conditions to the DR product under fed conditions is not a necessary prerequisite to a conclusion about the performance of the ER product under fed conditions because it is well

known that Depakote DR is essentially 100% bioavailable.

While this may be true, we are obviously equally concerned with the shape of the plasma-time curve, not just the total AUC. Indeed, a comparison of the performance of the DR product in the fed state (taken from a study in the original NDA for DR) and that of the ER product in the fed state suggests that the ER product may still result in a lower C_{min}. While we are not suggesting that such cross study quantitative comparisons are compelling, this does suggest that the simple fact that DR is completely available does not insure that the C_{mins} of the ER and DR are equivalent.

Finally, even if we assume that you have shown that the product performs reliably in the "fed" state, this does not insure that it will do so when patients eat meals which have varying effects on gastric emptying time. Specifically, you have studied the performance of the product under the presumed extremes of gastric emptying time (slowest, associated with a **standardized high fat meal**, and fastest, associated with no food). Assuming that gastric emptying time is the primary determinant of absorption and product performance, the failure of the product at the fastest extreme raises questions about when (in relation to the effects of various foods on emptying time) the product will begin to fail. That is, given that patients do not ingest standardized meals, we cannot know with confidence that taking the ER tablet "with meals" will be sufficiently analogous to the "fed" conditions in your study, and therefore, that the product will perform reliably. In short, there is no practical statement in labeling that can be constructed to achieve this end.

For these reasons, we have concluded that your proposal to label the product to be taken with food cannot be relied upon to prevent inadequate absorption.

In addition to the issues noted above, we have the following comments and requests. Although these issues were not reasons for our not approvable action, we would ask that you address them in your response to this letter.

Please also note that several of the following comments are related to biopharmaceutic and chemistry sections of labeling. We have included these comments because they were identified during this review cycle. However, other sections of labeling have not been fully evaluated at this time (as it is not our usual practice to review labeling in light of a not approvable action). We may have additional labeling comments at a later time.

Biopharmaceutics

1. In Study M95-401, which evaluated the effect of AEDs on the ER formulation bioavailability, the only AED that was adequately investigated was carbamazepine. This information should be reflected accordingly in the labeling.
2. In evaluating your proposed dissolution methodology and specification for Depakote ER, we estimate, using in vitro dissolution and in vivo absorption correlation, that the difference in the concentrations predicted from the lower boundary and upper boundary of the dissolution specification is more than $\frac{1}{10}$. This range is too wide to be acceptable.

Chemistry

Deficiencies Pertaining to the Drug Product:

1. Please provide the purity of _____ used in the manufacture of the drug product.
2. The table on page 94 in Volume 4 shows that the drug substance lot 10-213-AC and lot 09-066-CA were both used in the manufacturing of the stability batches 10-263-AR-04, 10-264-AR-04 and 10-265-AR-04. Were these two drug substance lots physically mixed to manufacture the stability batches 10-263-AR-04, 10-264-AR-04, and 10-265-AR-04?
3. Please define the acronym "BOP" in the sentence, "The procedures and limits for tablet weight are controlled by an in-plant BOP" which is on page 133 in Volume 4.
4. Please clarify: Are uncoated or printed tablets tested for hardness in the Document S41.07126(p. 19, Volume 6) and Standard Test Method S42P.0067 for Tablet Hardness(pp. 79 - 80 in Volume 6). Please correct this Standard Test Method S42P.0067 such that the type of tablet tested is clearly stated.
5. Please clarify: Are uncoated or printed tablets tested for thickness in the in Document S41.07126(p. 19, Volume 6) and Standard Test Method S42P.0066(pp. 77 - 78, Volume 6). Please correct the Standard Test Method S42P.0066 such that the type of tablet tested is clearly stated.

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9. Does the recoating procedure start with Section IV followed by Section V and finally Section VI as described on page 127 in Volume 4?
10. Please explain why the reference document S43D.07126 on page 74 in Volume 5 is "(PENDING)". Is this reference document S43D.07126 incomplete?
11. It is stated in the Table of Contents on page 11 in Volume 1 that Lot 10-263-AR-04 was used in the pivotal bioavailability study. Please provide the identification number of the pivotal bioavailability study to which this statement refers.
12. Please provide an _____ of the Divalproex Sodium — placebo, of the Sodium Hydrogen Divalproex(reference standard), and of the drug product.
13. Please clarify: Are uncoated or printed tablets used in the Document S42C.1705(p. 41, Volume 6) and Document S42C.1706(p. 45, Volume 6). Please correct Document S42C.1705 and Document S42C.1706 such that the type of tablets tested are clearly stated.
14. Please clarify: Are uncoated or printed tablets tested to determine the Content Uniformity? Please refer to the Standard Test Method S42C.1708 on pages 48 - 51 in Volume 6.

Deficiencies Pertaining to Labeling:

1. Please explain why the following inactive ingredients are listed in the Inactive Ingredient section in the draft labeling on page 7 of Volume 2. These inactive ingredients are not listed in the table on page 58 of Volume 2 (FD&C Blue No. 1; iron oxide; polydextrose; polyethylene glycol; propylene glycol; titanium dioxide and triacetin).
2. Please clarify pages 44-45 of Volume 12. Are there 100 tablets in the 6 x 6 professional sample or 36 tablets?
3. Please clarify pages 46-47 of Volume 12. Are there 100 tablets in the 3 x 10 professional sample or 30 tablets?

Recommendations Pertaining to Drug Product:

1. In future applications the Agency recommends that the drug product's regulatory specifications be provided in tabular form. This table should contain the drug product's tests, specifications, and the location of the test method.
2. In future applications the Agency recommends that the content of the application is consistent with the listing in the Table of Contents. For example, on page 14, Volume 2 Document S42C.1706 pertains to Content Uniformity however, in Document S41.07126, pp. 13 - 14, Volume 6, Document S42C.1706 isn't listed as one of the Standard Test Method.
3. In regards to the alternative packaging information on pages 231- 274 in Volume 5, the FDA recommends that after NDA 20-782 is approved, a Special-Supplement-Changes Being Effected for NDA 20-782 be submitted that contains all the information as recommended in the June 20, 1997 letter from Dr. Eric Sheinin and Dr. Douglas Sporn pertaining to the implementation of _____ bottles.
4. The following storage statement should be used in the HOW SUPPLIED section of the package insert:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

5. The following storage statement should be used on the label of the bottles containing 60, 100, and 500 tablets, respectively.

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[see USP Controlled Room Temperature]

6. The following storage statement should be used on the label of the single tablet blister.

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[see USP Controlled Room Temperature]

7. The following storage statement should be used on the label of the 100 tablet unit dose carton containing the ABBO-PAC® :

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[see USP Controlled Room Temperature]

8. The following storage statement should be used on the label of the 10 tablet professional sample bottle:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

9. The following storage statement should be used on the label of the 6 tablet professional sample bottle:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

10. The following storage statement should be used on the label of the 10 tablet professional sample bottle:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

11. The following storage statement should be used on the label of the 6 tablet professional sample bottle:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

12. The following storage statement should be used on the label of the 100 tablets 6 x 6 professional sample carton:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

13. The following storage statement should be used on the label of the 100 tablets 3 x 10 professional sample carton:

Store at 25°C(77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

Lastly, we have the following comments regarding the proprietary name for this product.

We note that you originally requested the proprietary name of Depakote TM. However, because you already have an approved product whose proprietary name is Depakote CP, the name, Depakote TM, for this product was found to be unacceptable. Consequently, following many discussions with the Division, you have proposed Depakote ER as the proprietary name for this product. We find this name to be acceptable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments 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.

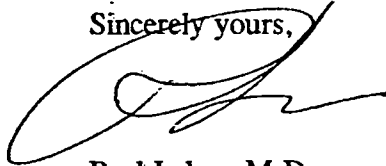
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-782
Page 10

If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Sincerely yours,



6/17/98

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

APPEARS THIS WAY
ON ORIGINAL

NDA 20-782

Page 9

cc:

Original NDA 20-782

HFD-120/Div. files

HFD-002/ORM

HFD-101/Office Director

HFD-810/ONDC Division Director

DISTRICT OFFICE

HFD-95/DDM-DIAB

HFD-120/J. Ware

HFD-120/Leber/Katz/Guzewska/Klein/Fitzgerald/Fisher

HFD-860/Sahajwalla/Yuan

HFD-340/Viswanathan/Yau

Handwritten notes:
5/13/98
6/15/98
5.6.98 incl 6/12/98
5/12/98
6/15/98

Drafted by: jhw/May 4, 1998/20782na.ltr

Initialed by:

final:

NOT APPROVABLE (NA)

APPEARS THIS WAY
ON ORIGINAL



NDA 20-782

Abbott Laboratories
Abbott Pharmaceutical Products Division
Attention: Steven E. Townsend
Project Manager, PPD Regulatory Affairs
100 Abbott Park Road, D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

Dear Mr. Townsend:

Please refer to your new drug application dated June 16, 1997, received June 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote ER (divalproex sodium extended-release tablets) 500mg.

We acknowledge receipt of your additional correspondence and amendments dated:

June 30, 1997	January 29, 1997	April 13, 1998
July 25, 1997	February 5, 1998	May 21, 1998
October 13, 1997	February 9, 1998	May 28, 1998
October 23, 1997		

The User Fee goal date for this application is June 17, 1998.

This original new drug application provides for an extended-release formulation of divalproex sodium which will allow for a once-daily dosing regimen as compared to an already marketed preparation of divalproex sodium (Depakote Delayed-Release Tablets).

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). Our reasons are as follows.

You have performed two definitive bioequivalence studies that compare the pharmacokinetics of the Depakote ER and Depakote Delayed-Release (DR) preparations. Study M95-376 was performed in healthy volunteers not receiving concomitant antiepileptic drugs (AEDs) and evaluated the pharmacokinetics of the ER formulation in the fed and fasted state compared to the DR formulation given in the fasted state. Study M95-401 was performed in patients with epilepsy who were receiving a concomitant AED; all treatments were given in the fed state.

In Study M95-401, the ER and DR preparations of divalproex sodium were shown to fall within 80 - 125% range of 90% confidence interval (CI).

In Study M95-376, the AUCs of the ER and DR preparations were equivalent. The C_{max} of the ER in the fasted state was low compared to that of the DR preparation, and failed standard equivalence criteria. This lower C_{max} is not a problem, because, as you know, the Division has agreed that valproate products designed to be given less frequently than available products can be considered equivalent to those marketed products if the AUCs are the same, but fluctuations in plasma levels are less (lower C_{max} and greater C_{min}).

However, the C_{min} of the ER formulation in the fasted state is also lower than the C_{min} of the DR marketed preparation, and does not fall within 80 - 125% range of 90% CI. Inspection of the individual patient data reveals two patients, Patients 5 and 10, whose Day 6 plasma concentration-time curves for the fasted ER treatment regimen demonstrate that plasma valproate levels are consistently lower throughout the day than the C_{min} for the DR tablet. This pattern of data suggests unacceptable product performance. (It is important to note that Depakote is approved as monotherapy for various seizure types; because of this, we believe the study in healthy subjects not receiving concomitant AEDs is an appropriate test system in which to evaluate the performance of the ER product).

For these reasons, we cannot conclude that the ER product has been shown to be equivalent to the marketed Depakote tablet.

We have reviewed your amendment dated May 21, 1998 which is intended to address this concern. In that amendment, you assert that the product might not perform adequately in a "... small subset of patients...", related to the rapid gastric emptying time associated with the fasted state. For this reason, you urge us to approve the product with labeling that advises that the product should be given with food.

Assuming that the poor performance of the product was, in fact, related to gastric emptying time (a point which you have not proved), we still find that your proposed solution is inadequate to insure acceptable product performance.

First, we disagree that the demonstration of an acceptable plasma time concentration profile in the fed state adequately insures that the product will perform adequately in the wider population of "fed" patients. Our concern arises from the fact that the product performed poorly in 2/14 fasted patients, an incidence that we cannot agree constitutes a small subset. Given this rate of failure, we are not convinced that the demonstration of reasonable performance in only 14 fed patients (the same patients, of course) is sufficiently robust to erase the concern raised by the poor performance in 2 of these subjects under different conditions.

Further, you assert that a direct comparison of the performance of the ER product under fed conditions to the DR product under fed conditions is not a necessary prerequisite to a conclusion about the performance of the ER product under fed conditions because it is well

known that Depakote DR is essentially 100% bioavailable.

While this may be true, we are obviously equally concerned with the shape of the plasma-time curve, not just the total AUC. Indeed, a comparison of the performance of the DR product in the fed state (taken from a study in the original NDA for DR) and that of the ER product in the fed state suggests that the ER product may still result in a lower C_{min}. While we are not suggesting that such cross study quantitative comparisons are compelling, this does suggest that the simple fact that DR is completely available does not insure that the C_{mins} of the ER and DR are equivalent.

Finally, even if we assume that you have shown that the product performs reliably in the "fed" state, this does not insure that it will do so when patients eat meals which have varying effects on gastric emptying time. Specifically, you have studied the performance of the product under the presumed extremes of gastric emptying time (slowest, associated with a **standardized high fat meal**, and fastest, associated with no food). Assuming that gastric emptying time is the primary determinant of absorption and product performance, the failure of the product at the fastest extreme raises questions about when (in relation to the effects of various foods on emptying time) the product will begin to fail. That is, given that patients do not ingest standardized meals, we cannot know with confidence that taking the ER tablet "with meals" will be sufficiently analogous to the "fed" conditions in your study, and therefore, that the product will perform reliably. In short, there is no practical statement in labeling that can be constructed to achieve this end.

For these reasons, we have concluded that your proposal to label the product to be taken with food cannot be relied upon to prevent inadequate absorption.

In addition to the issues noted above, we have the following comments and requests. Although these issues were not reasons for our not approvable action, we would ask that you address them in your response to this letter.

Biopharmaceutics

1. In Study M95-401, which evaluated the effect of AEDs on the ER formulation bioavailability, the only AED that was adequately investigated was carbamazepine. This information should be reflected accordingly in the labeling.
2. In evaluating your proposed dissolution methodology and specification for Depakote ER, we estimate, using in vitro dissolution and in vivo absorption correlation, that the difference in the concentrations predicted from the lower boundary and upper boundary of the dissolution specification is more than — This range is too wide to be acceptable.

Chemistry

Deficiencies Pertaining to the Drug Product:

1. Please provide the purity of _____ used in the manufacture of the drug product.
2. The table on page 94 in Volume 4 shows that the drug substance lot 10-213-AC and lot 09-066-CA were both used in the manufacturing of the stability batches 10-263-AR-04, 10-264-AR-04 and 10-265-AR-04. Were these two drug substance lots physically mixed to manufacture the stability batches 10-263-AR-04, 10-264-AR-04, and 10-265-AR-04?
3. Please define the acronym '_____' in the sentence, "The procedures and limits for tablet _____" which is on page 133 in Volume 4.
4. Please clarify: Are uncoated or printed tablets tested for hardness in the Document S41.07126(p. 19, Volume 6) and Standard Test Method S42P.0067 for Tablet Hardness(pp. 79 - 80 in Volume 6). Please correct this Standard Test Method S42P.0067 such that the type of tablet tested is clearly stated.
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14. Please clarify: Are uncoated or printed tablets tested to determine the Content Uniformity? Please refer to the Standard Test Method S42C.1708 on pages 48 - 51 in Volume 6.
15. Please clarify: In the Release Testing Requirement table provided by facsimile on 7/28/97 from Mr. Steven Townsend, Project Manager to Maryla Guzewska, Ph.D. it states that the Drug Release testing is conducted _____. However, in Document S41.07126 on page 15 in Volume 6 it states that the Drug Release is conducted on _____.
16. Please refer to Document S41.07126 page 15 - 17 in Volume 6: Why are there two standard test methods listed for Drug Release?
17. Please refer to page 12 in Volume 8: Please explain why there are two different dissolution methods, initial and final, being applied.
18. Please provide a list of all the container/closure systems that are currently being planned to be marketed. Also, include all the professional sample container/closure systems.

19. Are all the following blister packaging which are referred to on pages 35 - 38 and pages 42 - 43 in Volume 12 comprised of the same materials: Single tablet blister; 100 tablet ABBO-PAC® ; 10 tablet professional sample blister; 6 tablet professional sample blister?
20. Does the modified _____ described in Document S01.985359 (peelable blister packaging) on page 191 in Volume 5 comply with the 21 CFR, section 175.300?
21. Does the modified _____ described in Document S01.985360 (push-thru blister packaging) on page 196 in Volume 5 comply with the 21 CFR, section 175.300?
22. Refer to Document S01.633004 on page 160 in Volume 5: Why are two different _____ clear and gold, listed for the inside of the _____ cap?
23. Please explain the dissolution specification "DLP-93-032: Mean of 6 tablets release NMT _____ LC in 5 hours" which is located in the stability section of the NDA application.

Deficiencies Pertaining to Labeling:

1. Please explain why the following inactive ingredients are listed in the Inactive Ingredient section in the draft labeling on page 7 of Volume 2. These inactive ingredients are not listed in the table on page 58 of Volume 2 (FD&C Blue No. 1; iron oxide; polydextrose; polyethylene glycol; propylene glycol; titanium dioxide and triacetin).
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[see USP Controlled Room Temperature]

5. The following storage statement should be used on the label of the bottles containing 60, 100, and 500 tablets, respectively.

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7. The following storage statement should be used on the label of the 100 tablet unit dose carton containing the ABBO-PAC® :

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[see USP Controlled Room Temperature]

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[see USP Controlled Room Temperature]

9. The following storage statement should be used on the label of the 6 tablet professional sample bottle:

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We note that you originally requested the proprietary name of Depakote —. However, because you already have an approved product whose proprietary name is Depakote CP, the name, Depakote — for this product was found to be unacceptable. Consequently, following many discussions with the Division, you have proposed Depakote ER as the proprietary name for this product. We find this name to be acceptable.

NDA 20-782

Page 9

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments 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.

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If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Sincerely yours,

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

NDA 20-782

Page 10

cc:

Original NDA 20-782

HFD-120/Div. files

HFD-002/ORM

HFD-101/Office Director

HFD-810/ONDC Division Director

DISTRICT OFFICE

HFD-95/DDM-DIAB

HFD-120/J. Ware

HFD-120/Leber/Katz/Guzewska/Klein/Fitzgerald/Fisher

HFD-860/Sahajwalla/Yuan

HFD-340/Viswanathan/Yau

Drafted by: jhw/May 4, 1998/20782na.ltr

Initialed by:

final:

NOT APPROVABLE (NA)

APPEARS THIS WA.
ON ORIGINAL



ABBOTT

Ware

Pharmaceutical Products Division

Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157

November 13, 2002

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Ave.
Rockville, MD 20852

**RE: Depakote® ER
(Divalproex Sodium
Extended-Release) Tablets
NDA No. 20-782**

**Response to FDA Request for
Information**

Dear Dr. Katz,

The applicant, Abbott Laboratories, submits herewith a minor amendment to our pending application for Depakote® ER (Divalproex Sodium Extended-Release) Tablets, in accordance with the provisions of Section 505 (i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.

Reference is made to an October 25, 2002 request from Jackie Ware, Pharm.D., of your staff, to provide stability data for plasma samples stored at -20°C or -80°C for studies M01-274 and M00-232; and copies of references 1 and 2 identified in Volume 7 (page 234) included in our June 26, 2002 submission. Reference is also made to November 12, 2002 telephone conversations with Dr. Tandon and Dr. Ware, regarding the requested information. Based on those discussions it was agreed that Abbott's response would be limited to summary tables of the stability data and reference 1 from the information originally requested. A copy of the stability data was provided to Dr. Ware by facsimile on November 12, 2002.

Accordingly, this submission contains:

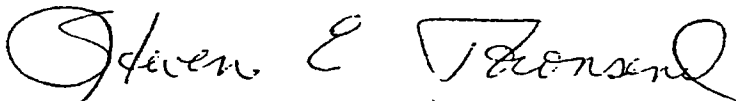
1. Stability data for plasma samples stored at -80°C for study M01-274
2. Stability data for plasma samples stored at -20°C for study M00-232
3. Reference 1 (R&D/02/242 Appendix 16.1_14 Drug Concentration Assay-Analytical Report, page 9) entitled; "The Determination of Valproic Acid Concentration in Human Plasma by _____, Abbott Study No. F90-196: ORS Lot Number 202941

Depakote ER
(Divalproex Sodium Extended-Release Tablets)
NDA 20-782
November 13, 2002
Page 2

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

Sincerely,

ABBOTT LABORATORIES



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

SET
Enclosure

Copy of cover letter to:

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

Copy of the submission to:

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