CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-168

Administrative Documents

(13.0)

Patent Information

(13.0) PATENT INFORMATION

Divalproex Sodium is covered by Patent Number 4988731. Patent Number 4988731 expires January 29, 2008. The Depakote ER formulation is covered by Patent Number 4913906. Patent Number 4913906 expires April 3, 2007.

Exclusivity Summary for NDA 21-168

NDA:	**21-168**
Trade Name:	**Depakote ER**
Generic Name:	**divalproex sodium**
Applicant Name:	**Abbott**
Division:	**HFD-120**
Project Manager:	**Lana Y. Chen, R.Ph.**
Approval Date:	**August 4, 2000**

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**
b.	Is it an effectiveness supplement? If yes, what type? (SE1, SE2, etc.)	**No**
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**
	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.	**N/A**
	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:	**N/A**
d.	Did the applicant request exclusivity?	**No**
	If the answer "yes," how many years of exclusivity did the applicant request?	
e.	Has pediatric exclusivity been granted for this Active Moiety?	**No**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

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) **No**

   If yes, what is NDA number

   If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? **No**

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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. **Yes**

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.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **18-723 19-680**

2. Combination product. **N/A**

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.)

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

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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**

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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.

   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**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

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? **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. **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? **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 #: **M98-845**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 **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: **N/A**

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 **No**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study: **N/A**

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 Study #: **M98-845**

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 applieant identified on the

FDA 1571 as the sponsor?

Investigation #1 IND#: — **Yes**

If 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? **N/A**

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.) **No**

If yes, explain:

/S/ for 8/4/00

Lana Y. Chen, R.Ph.
Project Manager
DNDP, HFD-120

/S/ 8/11/00

Russell Katz, M.D.
Director
DNDP, HFD-120

Form OGD-011347, Revised 10/13/98
c:\wpfiles\depakote.nda\excl_sum.doc
Final: August 4, 2000

cc:
Original NDA
Division File
HFD-120/Chen
HFD-93/Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21168	**Trade Name:**	DEPAKOTE (DIVALPROEX) ER 500MG TABLETS
Supplement Number:		**Generic Name:**	DIVALPROEX SODIUM
Supplement Type:		**Dosage Form:**	Tablet, Extended Release; Oral
Regulatory Action:	AP	**Proposed Indication:**	prophylaxis of migraine headaches in adults

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_ Other Age Groups (listed): 12 to 17 years

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Deferred studies for approved indication in pediatric patients age 12 to 17 until August 1, 2005; waiver granted for studies in pediatric patients under 12 years of age.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JACKIE WARE

/S/

Signature

Aug. 4, 2005

Date

Certification Requirement for all Applications

For Approval of a Drug Product

Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "A certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections(a) or (b) (Sections 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act), in connection with this application for approval of a drug product."

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

Steven E. Townsend

9/30/99

Steven E. Townsend
Associate Director, Pharmaceutical Products Division
Regulatory Affairs
Dept. 491, Bldg. AP6B-1
(847) 938-9547
100 Abbott Park Road
Abbott Park, Illinois 60064-6108

Date

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

MEMORANDUM

DATE: August 2, 2000

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

TO: File, NDA 21-168

SUBJECT: Action Memo for NDA 21-168, for the use of Depakote ER (divalproex sodium extended release) Tablets as prophylaxis of migraine headache

NDA 21-168, for the use of Depakote ER (a divalproex sodium tablet to be given once a day) as prophylaxis of migraine headaches, was submitted by Abbott Laboratories on 9/30/99. The only dosage form is a 500 mg tablet. The submission contained the report of a single randomized controlled trial, as well as CMC and biopharmaceutics data. Depakote Delayed Release Tablets, a dosage form given twice a day, are already approved for migraine prophylaxis (based on 2 randomized controlled trials). The application was reviewed by Dr. Armando Oliva, medical reviewer (reviews dated 6/7/00 and 8/1/00), Dr. Kallappa Koti, statistician (review dated 6/24/00), Dr. Maria Sunzel, biopharmaceutics (review dated 7/24/00), and Dr. Thomas Broadbent (reviews dated 7/20/00 and 8/3/00). All reviewers recommend that the application be approved.

In this memo, I will briefly review the results of the single controlled trial and explain the basis for the Division's action.

Study M98-845

This was a randomized, parallel group, double blind trial performed in 24 centers in the US. Patients with migraine headaches (with or without other headache types) were randomized to receive either Depakote ER or placebo. The trial consisted of a 4 week prospective baseline phase, a 12 week double blind phase, and a 1 week termination phase. Treatment was initiated at 500 mg once/day. After one week, the dose was supposed to be increased to 1000 mg/day for the remainder of the 12 week treatment phase. If this dose was not tolerated, the dose could be decreased to 500 mg/day for the remainder of the treatment phase. Patients were to keep a record of their headaches in a daily diary.

The primary outcome measure was the reduction from baseline in the 4 week migraine headache rate. The primary statistical test to be applied was to be the van Elteren test.

A total of 237 patients were randomized and treated and included in the primary ITT analysis (Placebo-115, Depakote ER-122). About 80% of patients, approximately equally distributed in the 2 treatment groups, completed the trial. The results of the analysis of the primary outcome measure are presented below (taken from Dr. Oliva's Table 11, page 20).

	Pbo	Depakote ER
Baseline	4.85	5.36
Treatment	4.52	3.94
Change	-0.33	-1.42

The p-value (t-test as perfomed by Dr. Oliva) for this comparison was 0.014. The p-value by the van Elteren test was 0.006 (see Dr. Koti's review, page 8).

The numbers in the table below represent an analysis of the data in which Dr. Oliva counted migraine headaches as separate events if the patient reported them as separate attacks. The sponsor counted a headache as a single headache if 2 or more events occurred within 24 hours in the same study period. In either case, the analysis yielded a statistically significant difference between drug and placebo.

In addition to the above results, the difference between drug and placebo treated patients also reached statistical significance within each of the 3 months of the study (see Dr. Oliva's review, page 15). A total of 94% of patients (96.5% of placebo patients, and 88.5% of Depakote ER patients) used the 1000 mg/day dose).

Interestingly, the average duration of migraine headaches that did occur was essentially the same in both treatment groups (Placebo-9 hours, Depakote-9.5 hours), and there was an equivalent number of patients in each group (6-7%) who had migraine rate reductions of at least 75%.

Regarding safety, no new safety concerns were noted. Although as can be seen from Dr. Oliva's Tables 22 and 23, there were a number of nominally significant comparisons between drug and placebo in mean changes from baseline in various lab measurements, almost all were quite small (only a decrease in platelet count of about 24 x 10^9/L appeared potentially clinically meaningful and this is already in labeling), and there were essentially no differences between drug and placebo in the proportion of patients who met pre-defined outlier criteria. In addition, the lowest platelet count recorded was 110,000.

Further, it is of note that Depakote ER is not bioequivalent to Depakote DR. Both Cmax and Cmin were lower with the ER than the DR, and the AUC was about — that of the DR.

Further, I agree with Dr. Oliva (see his memo of 8/1/00) that we can defer pediatric studies at this time, but that ultimately the sponsor will need to perform studies in patients with migraine down to the age of 12.

Finally, the chemists have reviewed the carton labeling, and note that on the sample boxes to be given to physicians (but not on the boxes to be sold to pharmacies) there are statements relating to indication [redacted]. We have spoken to Lisa Stockbridge of DDMAC in a phone conversation on 8/3/00. She informs us that this practice has been permitted, but in such cases, the package insert must accompany every box that contains this language. We have told this to the sponsor, who agrees.

The review team has discussed proposed labeling with the sponsor, most recently on 8/4/00, and we have reached agreement on the language to be adopted.

For this reason, I will issue the attached Approval letter.

/S/

Russell Katz, M.D.

Cc:
NDA 21-168
HFD-120
HFD-120/Katz/Oliva/Fisher/Fitzgerald/Broadbent/Guzewska
HFD-860/Sunzel

REGULATORY AFFAIRS
FAX TRANSMITTAL FORM

Date: February 23, 2000

To: Lana Chen, R.Ph.

Of: Regulatory Management Officer
Division of Neuropharmacological Drug Products
HFD-120
Food and Drug Administration
Rockville, MD 20857

Fax: (301) 594-2859

Pages: 2, including this cover sheet.

From: Steven E. Townsend
Associate Director, PPD, Regulatory Affairs
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Telephone: (847) 938-9547
Fax: (847) 937-8002

RE: NDA 21-168 Depakote ER

FOR RECEIVING FAX OPERATOR: Please call for pickup.

Dear Ms. Chen:

Attached is the M98-845 patient diary proposal we discussed during our February 14, teleconference. As I indicated on the phone this afternoon, I will also be sending a hard copy of this proposal as General Correspondence to NDA 21-168. Please contact me if you have any questions.

Sincerely,

Steven Townsend
SET/vch

NDA 21-168 Depakote ER Study M98-845 Diary Data Proposal

Reference is made to our Monday, February 14, 2000 teleconference between representatives of the Division of Neuropharmacological Drug Products and Abbott Laboratories regarding patient diaries from Study M98-845 and the information used to classify individual headaches as migraine vs. non-migraine. During that teleconference Abbott was requested to provide a proposal, for Agency consideration, for providing a subset of the patient diary data for review to confirm the headache classifications.

Accordingly, we propose to provide the following:

Patient Diary Data Subset

The patient diary data for a subset of randomly selected patients from each of the 24 investigator sites in Study M98-845 will be provided. This subset will include 64 patients which represents 27% of the 234 patients in the intent-to-treat data set. The 64 patients will consist of one patient from each treatment group (two patients total) for each of the 16 investigators who contributed 10 or fewer patients and two patients from each treatment group (four patients total) for each of the 8 investigators who contributed 11-20 patients.

Hard copies of the original 8.5 x 14 inch (legal sized paper) diaries would be provided on 8.5 x 11 inch standard paper (approximately 1300 double sided pages) for each of the selected patients.

In addition, diary data corresponding to each headache event will be supplied in a SAS transport file for each of the selected patients. The data included for each event will at a minimum include the headache's characteristics, peak intensity, and other variables (i.e. investigator, patient, visit, and event numbers) necessary to combine these data with the data set containing the headache CRF data previously provided. Please note that a majority of the diary data currently exists in the SAS transport files provided in our original application. Additional dialogue on the data structure may be required.

Patient Selection Method

The 64 patients will be randomly selected by first assigning each patient in the intent-to-treat data set a random (decimal) number between 0 and 1 using the SAS UNIFORM function. This function, once supplied an appropriate seed number, will be executed for each patient and will return a number generated from the uniform distribution on the interval (0,1). The patients selected from each investigator and treatment group will be the (one or two) patients with the smallest assigned numbers.

A seed number is needed to generate the random number for the first patient, and based on this number, the computer will generate the seed number for each subsequent patient. We would like to initiate the patient selection process as soon as possible. Therefore, we are requesting that the Division inform Abbott by Wednesday, March 1, 2000 of the acceptability of this proposal and if the Division would prefer to select the seed number to initiate the SAS function. Please note that in order to replicate the patient numbers selected via the SAS Uniform function, the seed number supplied should be an integer number greater than 0.

chen

FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

DATE: **February 22, 2000**
TIME:

DELIVER TO: **Steve Townsend**
Fax Number: 847.937.8002

FROM: Lana Chen, R. Ph. (Ph 301.594.5529)
Regulatory Management Officer.

Total number of pages, including cover page: 5

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

RE: NDA 21-168 Depakote ER

Please see attached for a migraine algorithm.

Thanks,
Lana

Classification of Individual Headaches in Migraine Studies

This document proposes an algorithm to classify individual headaches in migraine studies. The algorithm is based on the application of established IHS diagnostic criteria for migraine disorders. In order to classify individual headaches as migraine, the IHS criteria require some modification because some criteria either do not apply or are impractical to apply to individual headaches.

In order to understand the development of the algorithm, it is important to review the established IHS diagnostic criteria for migraine disorders. It is important to remember that the algorithm should only be used to classify headaches reported by subjects who have already met IHS criteria at study entry.

IHS criteria 1.1 for a "Migraine without Aura" diagnosis require the following:

A. At least 5 attacks fulfilling B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). In children below age 15, attacks may last 2-48 hours. If the patient falls asleep and wakes up without migraine, duration of attack is until time of awakening.

C. Headache has two of the following characteristics:
   1. unilateral location
   2. pulsatile quality
   3. moderate or severe intensity (inhibits or prohibits physical activity)
   4. aggravation by walking stairs or similar routine physical activity

D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

E. At least one of the following:
   1. history, physical, and neurological examinations do not suggest one of the disorders listed in groups 5-11 (not shown here)
   2. history and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

Criterion 1.1A does not apply to individual headaches.

Criterion 1.1B presents a problem and should not be applied to individual headaches. In an acute migraine trials, the duration of the migraine may be less than 4 hours if the episode is successfully treated with study medication. Therefore, it would be inappropriate to decide that a headache is not a migraine simply because of its short duration in such a setting. In migraine prophylaxis studies, subjects are allowed to take abortive or medications for their migraines. There again, a migraine may last less than 4 hours due to successful treatment. Therefore, the duration of the headache in these studies cannot be used to identify individual migraines.

Criterion 1.1C and 1.D can easily be applied to individual headaches, provided appropriate characteristics for each headache are recorded in the patient headache diary.

Criterion 1.1E is impractical to apply to individual headaches because it would require medical re-evaluation during or after each incident. Subjects have already met this criterion (or the corresponding criterion for migraine with aura) at study entry.

IHS criteria 1.2 for a "Migraine with Aura" diagnosis requires the following:

A. At least 2 attacks fulfilling B

B. At least 3 of the following 4 characteristics:
   1. one or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction
   2. at least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
   3. no aura symptoms lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
   4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).

C. At least one of the following:
   1. history, physical, and neurological examinations do not suggest one of the disorders listed in groups 5-11 (not shown here)
   2. history and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

Criterion 1.2A does not apply to individual headaches.

Criterion 1.2B is impractical to apply to individual headaches because it is unreasonable to collect such detailed information about the aura for each headache during a clinical trial. It seems safe to assume that subjects that experience an aura with their headaches in clinical trials have already met criterion 1.2B at study entry. Therefore, it does not appear necessary to apply 1.2B to individual headaches other than to identify whether or not an aura was present during the headache.

Criterion 1.2C is also impractical to apply to individual headaches for the same reason given for 1.1E above.

In order to apply the algorithm, it is necessary that appropriate headache characteristic data be collected in the patient diary. Table 1 lists the minimum data elements required for classification.

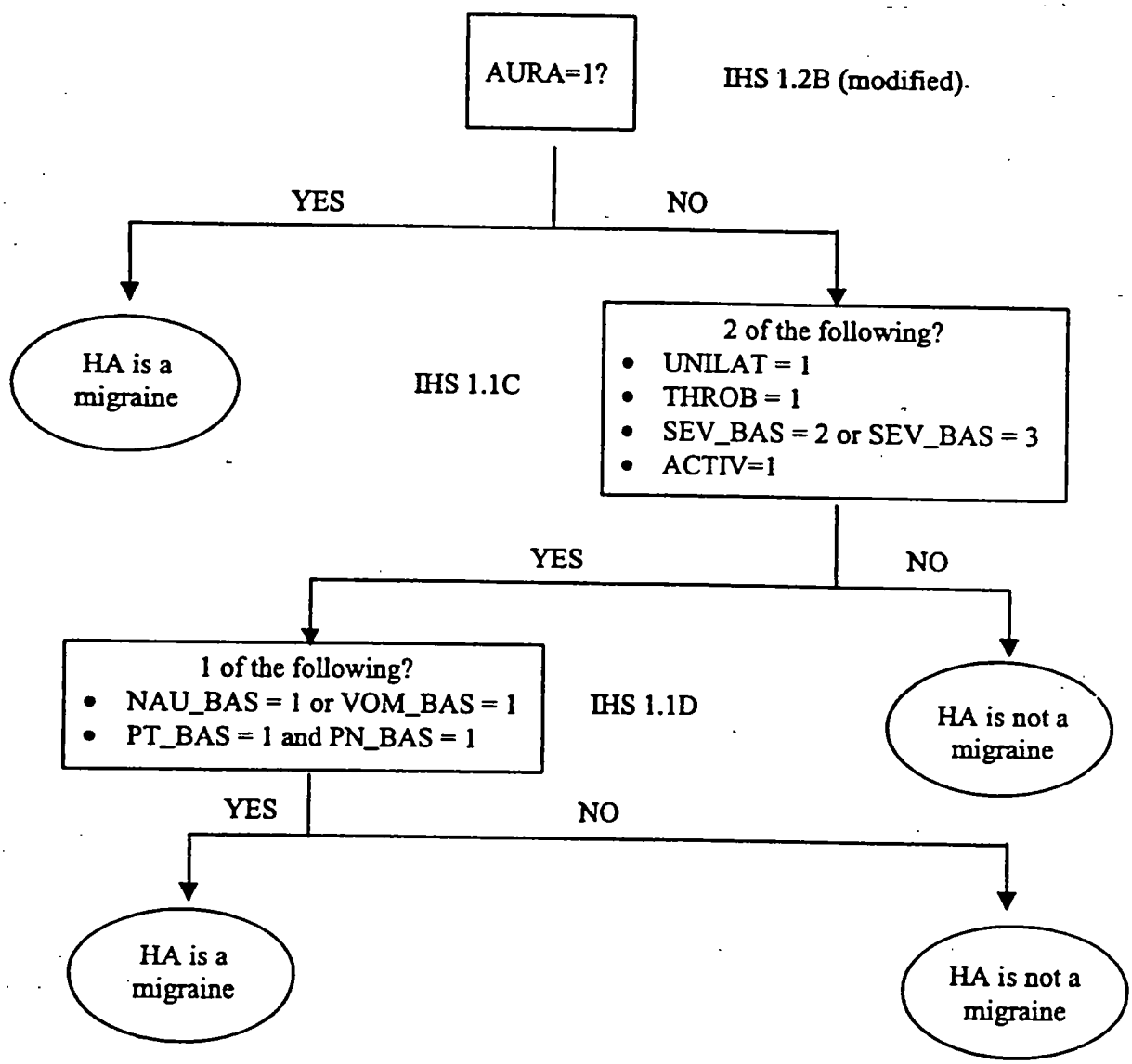
Table 1: Headache Characteristics

Variable Name	Variable Label	Format	Decode	Comment
DUR	Headache Duration	Number	Minutes or Hours	Duration of headache (may be collected data, or derived from start/stop date/time
AURA	Is aura present?	Number	0=no 1=yes	
SEV_BAS	Baseline Pain Severity	Number	0=none 1=mild 2=moderate 3=severe	Baseline pain severity prior to initial dose
NAU_BAS	Baseline Nausea	Number	0=absent 1=present	
VOM_BAS	Baseline Vomiting	Number	0=absent 1=present	
PT_BAS	Baseline Photophobia	Number	0=absent 1=present	
PN_BAS	Baseline Phonophobia	Number	0=none 1=present	
UNILAT	Is the baseline pain unilateral?	Number	0=no 1=yes	
THROB	Is pain throbbing or pulsating?	Number	0=no 1=yes	
ACTIV	Is the baseline pain worsened by physical activity?	Number	0=no 1=yes	aggravation by walking stairs or similar routine physical activity

Taking these considerations in mind, the algorithm, based on "modified IHS criteria" is shown in Figure 1. If the headache has an aura, then it's a migraine. If there is no aura, then the headache must meet criteria 1.1C and 1.1D in order to be classified as a migraine.

Again, it is emphasized that the algorithm should only be used to classify headaches reported by subjects who have already fully met at least one of the IHS criteria at study entry.

Figure 1: Classification of Individual Headaches in Migraine Studies



CC: NDA 21-168

Div File

HFD-120/Levin/Oliva/Chen AD 2/22/00
RL 2/22/00

Financial Disclosure by Clinical Investigators

Abbott Laboratories is submitting the following information under the provisions of 21 CFR 54.4. Provided in this section is a Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators covering clinical study M98-845.

This section is organized in the following manner:

- Form FDA 3454
  - List of names of clinical investigators meeting the requirements of 21 CFR 54.2(a), (b) and (f).
  - List of names of clinical investigators where the sponsor was not able to obtain the information required under 21 CFR 54.2(b) from the investigators. The procedures taken to obtain this information, showing due diligence on the part of the sponsor, are provided.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached lists	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Jeanne Fox	Director, PPD, Regulatory Affairs
FIRM/ORGANIZATION	
Abbott Laboratories, Pharmaceutical Products Division	
SIGNATURE	**DATE**
Steven E. Ronsen for Jeanne Fox	9/30/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

Study M98-845 Certification: Financial Interests and Arrangements of Clinical Investigators

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(Replaced by Dr. Yataco 11/98)
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West Palm Beach, FL 33407

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

Note: Principal Investigator is bolded

M98-845 Due Diligence for Obtaining Financial Disclosure Information From Principle Investigators and Subinvestigators

The following procedure was followed when attempting to obtain financial disclosure information from principal investigators and subinvestigators. This information will be used for FDA Form 3454, Part 3 to certify Abbott has acted with due diligence in obtaining financial disclosure information for study M98-845 used to support and NDA Submission.

Principal Investigator (PI)

1. PI contacted via letter to inform him/her of the need to complete an Abbott Financial Disclosure Form (AFDF) for study M98-845 with which he/she was involved. The AFDF accompanied the letter.
2. PI contacted at least 3 times via telephone/facsimile if AFDF not received after first mailing.
3. PI sent certified letter requesting AFDF be completed and returned if AFDF not received after telephone/facsimile contacts.
4. If not response within 15 days after mailing of the certified or if PI refuses to sign AFDF, STOP.

Subinvestigator

1. PI contacted via letter to inform him/her of the need to complete an Abbott Financial Disclosure Form (AFDF) for study M98-845 with which his/her subinvestigators were involved. The AFDFs accompanied the letter.
2. At least 3 requests for AFDF via telephone/facsimile if subinvestigator's AFDF not received after first mailing.
3. PI contacted with request for subinvestigator's forwarding address, if appropriate.
4. If subinvestigator has left the institution and there is no forwarding information available, this will be documented.
5. Subinvestigator sent certified letter requesting AFDF be completed and returned if AFDF not received after telephone/facsimile contacts.
6. If not response within 15 days after mailing of the certified or if subinvestogator refuses to sign AFDF, STOP.

Study M98-845 Certification: Financial Interests and Arrangements of Clinical Investigators Due Diligence

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(Replaced by Dr. Yataco 11/98)
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West Palm Beach, FL 33407

*Principal Investigators is listed only to identify the site.

Table of Contents

NDA 21-168 Depakote ER (divalproex sodium) Tablets

Approval Package

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA:	**21-168**
Drug:	**Depakote ER (divalproex sodium) Extended ReleaseTablets**
Applicant:	**Abbott**
Chem/Ther/other Types:	**3S**
CSO/PM:	**Lana Y. Chen, R.Ph.**
Phone:	**301-594-5529**
Division:	**HFD-120**
USER FEE GOAL DATE:	**August 4, 2000 (10 month)**
CHECKLIST COMPLETE:	**July 17, 2000**

Arrange package in the following order (include a completed copy of this CHECKLIST):	**Check or Comment**
1. ACTION LETTER with supervisory signatures	Approval
Are there any Phase 4 commitments?	No
2. Have all disciplines completed their reviews?	Yes
3. LABELING (package insert and carton and container labels).	Yes (Draft)
4. PATENT INFORMATION	Yes
5. EXCLUSIVITY CHECKLIST	Yes
6. PEDIATRIC PAGE (all NDAs)	Yes
7. DEBARMENT CERTIFICATION	Yes
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES	Yes (inspections complete)
If AE or AP ltr, explain if not satisfactorily completed.	AP - Satisfactory
Attach a COMIS printout of DSI status.	Yes
If no audits were requested, include a memo explaining why.	N/A
9. REVIEWS & MEMORANDA:	
a. DIVISION DIRECTOR'S MEMO	Yes
b. GROUP LEADER'S MEMO	Yes
c. MEDICAL REVIEW	Yes
d. SAFETY UPDATE REVIEW	N/A (all studies complete at time of
e. STATISTICAL REVIEW	Yes
f. BIOPHARMACEUTICS REVIEW	Yes
g PHARMACOLOGY REVIEW (Include pertinent IND reviews)	Yes
1) Statistical Review of Carcinogenicity Study(ies)	Yes
2) CAC Report/Minutes	Yes
h. CHEMISTRY REVIEW	Yes
1) Labeling and Nomenclature Committee Review Memorandum	Yes
2) Date EER completed	June 28, 2000
3) EER Results (OK/NO) (attach signed form or CIRTS printout)	OK
4) FUR needed	No
5) FUR requested	N/A
6) Have the methods been validated?	No
7) Environmental Assessment Review	N/A
8) FONSI	N/A
i. MICROBIOLOGY REVIEW	N/A
1) What is the status of the monograph?	N/A
10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	Yes
11. MINUTES OF MEETINGS	
a. Date of End-of-Phase 2 Meeting	N/A
b. Date of pre-NDA Meeting	August 19, 1999
12. ADVISORY COMMITTEE MEETING	N/A
a. Meeting Conducted	
b. Minutes	
c. Info Alert	
d. Transcript	
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	None
14. If approval letter has ADVERTISING MATERIAL been reviewed?	No

Armando Oliva

. .:	Russell Katz
cc:	Maria Sunzel; Chandra Sahajwalla
Subject:	latest Depakote ER labeling

Here's the latest labeling, with the following changes:

1. Biopharm - Absorption section -- combined the results of the two multilple dose relative bioavailability studies with DR formulation.

2. Adverse effects - added statements that the AE's occurred more frequently than in placebo, and include a note sponsor to verify that this is true.

I bolded all notes to sponsor.

3. Dosage and Administration: added additional sentence that doses other than 1000 mg/day have not been studied, but the effective dose range for DR is 500-100 mg/day. Also, advised patients to use DR INSTEAD of ER (to avoid combined use) if smaller dose adjustments are necessary.


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000726 reviewer draft clean.do...

Armando Oliva, MD - Medical Officer (Neurologist)
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DHHS/FDA/CDER/ODEI/DNDP - WOC2 Room 4042
mail: olivaa@cder.fda.gov
one: (301) 594-5517 - Fax: (301) 594-2858

This version chng'd by Rusty. Faxed to them 7/26 3:45pm.

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

Armando Oliva

---

o: Russell Katz
Cc: Maria Sunzel; Chandra Sahajwalla; Thomas Broadbent; Maria Guzewska; Lana Chen
Subject: Updated Depaote ER labeling

Attached is the latest Depakote ER labeling. The first file shows the revisions. The second file is the clean running text. The following changes have been made from the last edition which we discussed this (Friday) morning:

1. Biopharm: the PK/absorption section has been rewritten. The first paragraph discusses absolute bioavailability. The second paragraph discusses relative bioavailability with DR tablet, and food effect. It describes the different study conditions under which those measurements were made in order to identifty possible factors that may explain why the relative bioavailability to DR is lower than the absolute bioavailability. The final paragraph describes dose fluctuations relative to DR and that the ER and DR are not bioequivalent.

2. Clinical Trials: I deleted the statement that ——— based on our discussion. I agree that this statement doesn't have to go in labeling. It also makes the text flow more smoothly when discussing the results of the ER study.

3. Precautions:Pediatric Use / Geriatric Use - I reworded it to be more in line with the labeling regs.

4. Adverse Events: I included a note to the sponsor...they should combine the unique AE's seen with DR mania and epilepsy trials and include it in the section "other patient populations."

5. Dosage and Administration: I deleted the statement about ——— to avoid conversion issues, but added a statement at the end that the ER and DR are not bioequivalent and refer the reader to the clin pharm, PK section. Under general dosing advice, I changed the advice to switch to another formulation of valproate for smaller starting doses (elderly, and gi irritated patients). Instead, they should switch specifically to DR because DR is the only other formulation approved for migraine prophylaxis.

6. How Supplied: I added the manufacturing information at the end of this section, as suggested by Dr. Guzewska.


000721 reviewer draft.doc


000721 reviewer draft clean.do...

Armando

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

Printed by Jackie Ware

Electronic Mail Message

Date: 02-Aug-2000 05:29pm
From: Meg Drew
meg.drew@secure.abbott.com
Dept:
Tel No:

TO: warej (warej@A1)

CC: Steven Townsend (Steven.Townsend@ln.ssw.abbott.com)
CC: James Steck (James.Steck@ln.ssw.abbott.com)
Subject: Draft Depakote ER Package Insert

lease find attached the most current version of the package insert which
ncorporates the revisions agreed upon this morning. They were as follows:

. PEDIATRIC USE: Deleted '
. ADVERSE REACTIONS - Other Patient Populations: Deleted last sentence
nder Gastrointestinal regarding
DOSING AND ADMINISTRATION: Deleted
from the second
aragraph and corrected spelling of "RELEASE" in penultimate paragraph.

APPEARS THIS WAY
ON ORIGINAL

RFC-822-headers:
Received: from cdswsl.cder.fda.gov
 (\"port 39597"@cdswsl.cder.fda.gov [150.148.150.21])
 by mail.cder.fda.gov (PMDF V6.0-24 #42130)
 with ESMTP id <01JSIJVWLJ4:94EZY8@mail.cder.fda.gov> for warej@cder.fda.gov;
 Wed, 02 Aug 2000 17:29:58 -0400 (EDT)
Received: from 63.77.7.240 by cdswsl.cder.fda.gov with ESMTP
 (Mercury Secure Server ESMTP Relay(WIN) v4.3); Wed, 02 Aug 2000 17:27:47 -0400
        ': from host240.abbott.com ([63.77.7.240])
         116 via smtpd (for cdswsl.cder.fda.gov [150.148.150.21])
          '; Wed, 02 Aug 2000 21:25:52 -0000 (UT)
          by host240.abbott.com id AA11298
          ch ESMTP Gateway 3.0 for warej@cder.fda.gov); Wed,
        2000 16:30:57 -0500
Received: by host246.abbott.com (Internal Mail Agent-4); Wed,
 02 Aug 2000 16:20:57 -0500
Received: by host246.abbott.com (Internal Mail Agent-3); Wed,
 02 Aug 2000 16:20:57 -0500
Received: by host246.abbott.com (Internal Mail Agent-2); Wed,
 02 Aug 2000 16:20:57 -0500
Received: by host246.abbott.com (Internal Mail Agent-1); Wed,
 02 Aug 2000 16:20:57 -0500
X-Server-Uuid: 6C79ffd4-893e-11d3-8ed3-0008c75df4f2
X-Server-Uuid: e6ac1cb3-f112-11d3-bd30-0008c7096111
X-SMIME-VPN: Processed
X-Mas-ID: 15966DC873C16-01-01
X-WSS-ID: 15966DC9905S03-01-01

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

facsimile TRANSMITTAL

To: Jackie Ware. Pharm.D.

Of: Food and Drug Administration

Fax: 1-301-594-2859

Pages: 21, including this cover sheet.

RE: NDA 21-168

Date: August 1. 2000

Jackie.

Following is the draft marked up version of the June 28. 2000 draft labeling for Depakote ER.

Please call if there are any questions.

JDS/wet Jim Steck

From the desk of ..

James Steck
Director
Abbott Laboratories
100 Abbott Park Rd.
D491/AP6B-1
Abbott Park, IL 60064-6108
Phone: 847-937-0335
Fax 847-937-8002

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

2.1

Proposed Text of Labeling

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