# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-168

# Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-168

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

AUG 4 2000

Dear Mr. Townsend:

Please refer to your new drug application (NDA) dated September 30, 1999, received October 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote ER (divalproex sodium extended-release) Tablets.

We acknowledge receipt of your additional correspondence and amendments dated:

| | | | |
|---|---|---|---|
| December 6, 1999 | January 31, 2000 | May 22, 2000 | August 2, 2000 (2) |
| January 5, 2000 | March 1, 2000 | July 6, 2000 (2) | |
| January 28, 2000 | April 28, 2000 | July 14, 2000 | |

This new drug application provides for the use of Depakote ER (divalproex sodium extended-release) Tablets for prophylaxis of migraine headaches in adults.

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

## Labeling

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (immediate container and carton labels submitted August 2, 2000). We note that this labeling was agreed to in the August 4, 2000 telephone conversation between Abbott representatives and this Division. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21168." Approval of this submission by FDA is not required before the labeling is used.

**Expiration**

The tentative expiration dating for Depakote ER tablets in all package presentations is 24 months at 25°C.

**Dissolution Method and Specification**

Your proposed dissolution method and specification, submitted September 30, 1999, is acceptable.

***In vitro–in vivo* Correlation**

A Type A *in vitro–in vivo* correlation has been established. The Type A *in vitro–in vivo* correlation may be used for waivers for *in vivo* bioequivalence studies of future manufacturing changes or new formulations according to *Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997.*

**Pediatric Studies**

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies in pediatric patients age 12 to 17 until August 1, 2005. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

We note that in your September 30, 1999 submission, you requested a partial waiver of the pediatric study requirement under 21 CFR 314.55(c). We have reviewed your request and are waiving the pediatric study requirement for studies of migraine headache prophylaxis in pediatric patients less than 12 years of age.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If

you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

**Methods Validations**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

**Promotional Material**

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

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

**Other**

Please submit one market package (containers and cartons only) of the drug product when it is available.

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

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/

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

Enclosure