



NDA 21-168 / S-012

Abbott Laboratories
Attention: Lee M. Muraoka, BSP Pharm, MS
Senior Regulatory Affairs Administrator
Global Pharmaceutical Regulatory Affairs
RA76, Building AP30-1E
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Dear Mr. Muraoka:

Please refer to your supplemental new drug application submitted October 25, 2004, received October 26, 2004 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote ER (divalproex sodium extended-release tablets) 250 mg and 500 mg.

This supplement proposes the use of Depakote ER as monotherapy in the treatment of acute manic or mixed episodes associated with bipolar I disorder, with or without psychotic features.

Please also refer to your amendments dated October 7, 2005 and October 20, 2005. Your October 7, 2005 response, received October 11, 2005, was a Complete Class 1 Response to our action letter of August 18, 2005.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Partial Waiver, Partial Deferral

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.

We are waiving this requirement for children below the age of 10 years. We are deferring submission of pediatric studies under PREA for children aged 10 to 17 years (children and adolescents), until October 7, 2007.

The deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitments are listed below.

Deferred pediatric studies under PREA.

1. You are required to assess the safety and effectiveness of Depakote ER in the treatment of bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents).

Final Report Submission: October 7, 2007

Please submit study protocols to your IND, and final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated “**Required Pediatric Study Commitments**”.

Please also note that, as of November 1, 2005, in accordance with the Electronic Labeling Rule [68 FR 69009 – 69020] the Agency has implemented an automated system to process, review and archive the contents of labeling in electronic [Structured Product Labeling, or SPL] format. The labeling in this pediatric supplemental NDA should conform to SPL and be submitted in accordance with the *SPL Implementation guide for FDA Content of Labeling Submissions* [available at URL <http://www.hl7.org/Special/committees/rcrim/index.cfm>]. Additional details on the content of labeling submissions may be found in the *Guidance to Industry: Providing Regulatory Submissions in Electronic Format – Content of Labeling*.

Pediatric Exclusivity

Please note that Proposed Pediatric Study Requests and Pediatric Written Requests, which apply to pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act, are distinct from, and may need to be developed *in addition to*, pediatric studies under PREA as described above. Satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Additional Phase 4 Commitments (Clinical and Biopharmaceutics):

We remind you of your additional postmarketing commitments, requested in our action letter of August 18, 2005 and agreed between yourselves and Dr. Doris Bates of this Division on December 1, 2005. The commitments are summarized below.

Clinical Efficacy and Safety: Adult clinical study to address longer-term efficacy and safety of Depakote ER in bipolar disorder.

2. We note your proposal to meet this commitment by submitting reports from six ongoing or completed studies using either Depakote or Depakote ER:

- two longer-term studies of efficacy and safety in adults with bipolar disorder [M92-822 and M99-045],
- two pediatric long-term studies in bipolar disorder [M02-555 and M03-647], and
- two additional studies which would be submitted for the provision of long-term safety data only [M02-547 and M02-551].

We have agreed to accept the proposed submission as a clinical efficacy supplement, but note that the pertinent study reports should be submitted together in a single submission. As described above, the accompanying labeling for this submission must be in SPL format.

Final Report Submission: December 1, 2009

Biopharmaceutics: Drug interaction studies with atypical antipsychotics.

In response to our request that you conduct and submit drug interaction studies examining the interaction of Depakote ER with atypical antipsychotics, you have proposed the following three post-approval commitments, to which we agree:

3. In vitro Study #1: Determination of the IC₅₀ for VPA (valproate) in human liver microsomes, with respect to the following five substrates:

aripiprazole
olanzapine
quetiapine
risperidone
ziprasidone

Final Report Submission: June 30, 2006.

4. In vitro Study #2: Evaluation of effect on glucuronidation of VPA (valproate) in activated human liver microsomes of the following five substrates:

aripiprazole
olanzapine
quetiapine
risperidone
ziprasidone

Final Report Submission: June 30, 2006.

5. Clinical Pharmacology Study: You have agreed to perform human clinical pharmacology studies to fully characterize any potential drug-drug interactions identified based on the results of In Vitro Studies #1 and #2. The likelihood of such interactions will be evaluated based on the PhRMA guidelines for drug-drug interaction (Bjornsson et. al., 2003).

Final Report(s) Submission: July 1, 2007.

Submit clinical protocols to your IND for this product. Submit nonclinical protocols and all final study reports to this NDA, including any final reports intended to support clinical efficacy claims or changes in labeling. Please note that all new original NDAs and efficacy supplements must now include labeling in electronic format that conforms to SPL (Structured Product Labeling) standards.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary for each commitment in your annual report to this NDA. The status summary should include:

- ◆ expected summary completion dates,
- ◆ expected final report submission dates,
- ◆ any changes in plans since the last annual report,
- ◆ and, for clinical studies, the number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled “**Postmarketing Study Protocol**”, “**Postmarketing Study Final Report**”, or “**Postmarketing Study Correspondence**.” Please clearly mark all submissions with the supplement number or numbers that they support, for database management purposes.

Labeling

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert), ^{(b) (4)}
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Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. We encourage you to consider formatting this FPL submission as SPL, but because this is not a new submission, it is not required.

Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission “**FPL for approved supplemental NDAs 21-168 / S-012**.” Approval of this submission by FDA is not required before the labeling is used.

Introductory Promotional Materials

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in this indication. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-796-1040.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: agreed-upon labeling [clean copy: (b) (4)
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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
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