DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018081/S-046/S-048/S-050/S-052
NDA 018082/S-031/S-033/S-035/S-037
NDA 018723/S-037/S-040/S-043/S-045/S-046
NDA 019680/S-025/S-027/S-029/S-031
NDA 020593/S-016/S-020/S-023
NDA 021168/S-016/S-017/S-020/S-022

SUPPLEMENT APPROVAL
REMS RETRACTION

Abbott Laboratories
Attention: Jeremy M. McCumber
Manager, Regulatory Affairs, Pharmaceuticals Products Group
200 Abbott Park Road
Dept PA 76 Bldg AP30-1
Abbott Park, Illinois 60064-6157

Dear Mr. McCumber:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Application	Drug Product	Submitted on:	Received on:
NDA 018081/S-046	Depakene (valproic acid) Capsules	12/28/2007	12/31/2007
NDA 018082/S-031	Depakene (valproic acid) Oral Solution		
NDA 018723/S-037	Depakote (divalproex sodium) Delayed Release Tablets		
NDA 019680/S-025	Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules)		
NDA 020593/S-016	Depacon (valproate sodium) Injection		
NDA 021168/S-016	Depakote ER (divalproex sodium) Extended Release Tablets		

These "Changes Being Effected" supplements provide for:

- Addition of information in Precautions section regarding Hypothermia
- Revision to the Precautions subsections - Hyperammonemia and Hyperammonemia and Encephalopathy associated with Concomitant Topiramate Use
- Revision of the Drug Interactions, Topiramate subsection
- Addition of information in Warnings section regarding drug interactions with Carbapenem Antibiotics

Application	Drug Product	Submitted on:	Received on:
NDA 018081/S-048	Depakene (valproic acid) Capsules	01/14/2009	01/15/2009
NDA 018082/S-033	Depakene (valproic acid) Oral Solution		
NDA 018723/S-040	Depakote (divalproex sodium) Delayed Release Tablets		
NDA 019680/S-027	Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules)		
NDA 021168/S-017	Depakote ER (divalproex sodium) Extended Release Tablets		
These "Prior Approval" supplements provide for:			
• Proposed REMS including Medication Guides • Inclusion of NAAED Pregnancy Registry information			

Application	Drug Product	Submitted on:	Received on:
NDA 018081/S-050	Depakene (valproic acid) Capsules	11/18/2009	11/18/2009
NDA 018082/S-035	Depakene (valproic acid) Oral Solution		
NDA 018723/S-043	Depakote (divalproex sodium) Delayed Release Tablets		
NDA 019680/S-029	Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules)		
NDA 020593/S-020	Depacon (valproate sodium) Injection		
NDA 021168/S-020	Depakote ER (divalproex sodium) Extended Release Tablets		
These "Changes Being Effected" supplements provide for:			
Information regarding the risk of developmental delay in the offspring of women exposed to valproate during pregnancy			

Application	Drug Product	Submitted on:	Received on:
NDA 018081/S-052	Depakene (valproic acid) Capsules	03/05/2010	03/05/2010
NDA 018082/S-037	Depakene (valproic acid) Oral Solution		
NDA 018723/S-045	Depakote (divalproex sodium) Delayed Release Tablets		
NDA 020593/S-023	Depacon (valproate sodium) Injection		
These "Prior Approval" supplements provide for:			
Revised product labeling to PLR format			

Application	Drug Product	Submitted on:	Received on:
NDA 018723/S-046	Depakote (divalproex sodium) Delayed Release Tablets	04/30/2010	04/30/2010
NDA 019680/S-031	Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules)		
NDA 021168/S-022	Depakote ER (divalproex sodium) Extended Release Tablets		
These "Prior Approval" supplements provide for:			
Warnings and Precautions section to include information regarding the potential for medication residue			

We acknowledge receipt of your amendments as follows:

Application	Amendments Dated:
NDA 018081/S-048 NDA 018082/S-033	February 05, 2009 and April 16, 2009
NDA 018723/S-040 NDA 019680/S-027 NDA 021168/S-017	February 05, 2009, February 26, 2009, and April 16, 2009

We have completed our review of these supplemental applications, and our review of labeling revisions for all aforementioned NDAs, as amended, as follows: adding information regarding the North American Antiepilepsy Drug Pregnancy Registry and strengthening language related to the risk for neural tube defects and other congenital malformations following in utero exposure to valproate (and cautioning against the treatment of women of childbearing potential as well as pregnant women with valproate due to these risks). These supplemental applications are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In our letter dated December 16, 2008, we notified you that a risk evaluation and mitigation strategy (REMS) is required for Depakene (valproic acid), Depakote (divalproex sodium), and Depacon (valproate sodium) to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs), of which Depakene (valproic acid), Depakote (divalproex sodium), and Depacon (valproate sodium) are members. We indicated that your REMS must include a Medication Guide and a timetable for submission of assessments of the REMS.

We acknowledge receipt of your proposed REMS as described in your January 15, 2009, February 6 and 27, 2009, and April 16, 2009 submissions. The proposed REMS, as amended, contains a Medication Guide and a timetable for submission of assessments of the REMS.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the REMS to ensure that the benefits of Depakene (valproic acid), Depakote (divalproex sodium), and Depacon (valproate sodium) outweigh their risks. Therefore, a REMS for Depakene (valproic acid), Depakote (divalproex sodium), and Depacon (valproate sodium) is not required. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

We remind you that the Medication Guide will be part of the approved labeling in accordance with 21 CFR 208.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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, call Jacqueline H. Ware, PharmD, Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
10/07/2011