

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-267

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Pediatric Research and Equity Act

NDA 22-267

Request for PeRC Concurrence:

- **Commitment Fulfilled**
- **No Further Studies Required under PREA for this Drug/Indication**

Product name and active ingredient/ dosage form:

Depakote ER (divalproex sodium) extended release tablets

NDA 22-267

Supplement Type: **not a supplement; Type 6 NDA**

Supplement Number: **not applicable**

HFD-130, Division of Psychiatry Products

Sponsor: **Abbott Laboratories**

Indications(s): **treatment of mania associated with bipolar disorder in children and adolescents aged 10 to 17**

Comments:

This NDA is a pediatric supplement submitted in response to a prior PREA Phase 4 Commitment [NDA 21-168, SE1-012, approved on 12-6-05. The terms of the commitment are as follows:

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

The December 6, 2005 approval letter for NDA 21-168 / S-012 waived this required study commitment for children aged 0 to 10 years.

The PEB meeting of December 14, 2007 determined that:

- *this NDA met the requirements of the Pediatric Written Request.*
- *exclusivity was granted.*

The Division of Psychiatry Products has reviewed NDA 22-267. The single efficacy study performed failed to demonstrate efficacy. The applicant is not seeking an efficacy claim, but must include safety data and relevant language in labeling, and has submitted labeling in Physician's Labeling Rule Format. DPP has concluded that the terms of the PREA Phase 4 Commitment have been met, and that there is no further requirement for pediatric studies in this indication.

DPP now seeks PeRC concurrence:

- *that the existing PREA commitment has been fulfilled and*
- *that there are no further PREA requirements applicable to this submission.*

**Cover Sheet to Forms 3542a
Patent Information Pursuant to 21 CFR 314.53 for NDA Number 21-168**

Tradename: Depakote® ER
Active Ingredient: Divalproex sodium
Strength: 250 mg and 500 mg
Dosage Form: Tablet, Extended-Release
Name of Patent Owner: Abbott Laboratories

The attached Forms 3542a are provided in accordance with 21 CFR 314.53 and reflect relevant patent information as already shown in the FDA Orange Book. The patents for which these forms are submitted can be summarized as follows:

U.S. Patent No.	Expiration Date	Type of Patent
4,988,731	January 29, 2008	Drug Substance, Drug Product
5,212,326	January 29, 2008	Drug Substance, Drug Product
6,419,953 *	December 18, 2018	Drug Product, Method-of-Use
6,511,678	December 18, 2018	Drug Product, Method-of-Use
6,528,090	December 18, 2018	Drug product
6,528,091 *	December 18, 2018	Method-of-Use
6,713,086	December 18, 2018	Drug Product, Method-of-Use
6,720,004	December 18, 2018	Drug product

(* Patent Nos. 6,419,953 and 6,528,091 are applicable to the 500 mg strength only.)

The above summary is intended for the convenience of the FDA only. In the event of a conflict between this sheet and the Forms 3542a submitted herewith, the latter control.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-168

NAME OF APPLICANT / NDA HOLDER

Abbott Laboratories

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Depakote® ER

ACTIVE INGREDIENT(S)

Divalproex sodium

STRENGTH(S)

250 mg and 500 mg

DOSAGE FORM

Tablet, Extended Release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,988,731

b. Issue Date of Patent

January 29, 1991

c. Expiration Date of Patent

January 29, 2008

d. Name of Patent Owner

Abbott Laboratories

Address (of Patent Owner)

100 Abbott Park Road, 377/AP6A-1

City/State

Abbott Park, Illinois

ZIP Code

60064-6008

FAX Number (if available)

847-938-2623

Telephone Number

847-937-6364

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. The patent claims, among others, the form of the drug substance in the drug product that is the subject of the approved NDA as well as the present NDA supplement and is submitted for listing on that basis, so no additional testing is required.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

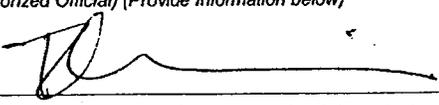
4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed September 5, 2007</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Robert DeBerardine</p>	
<p>Address Abbott Laboratories 100 Abbott Park Road, 377/AP6A-1</p>	<p>City/State Abbott Park, Illinois</p>
<p>ZIP Code 60064-6008</p>	<p>Telephone Number 847-937-6364</p>
<p>FAX Number (if available) 847-938-2623</p>	<p>E-Mail Address (if available)</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-168

NAME OF APPLICANT / NDA HOLDER

Abbott Laboratories

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Depakote[®] ER

ACTIVE INGREDIENT(S)

Divalproex sodium

STRENGTH(S)

250 mg and 500 mg

DOSAGE FORM

Tablet, Extended Release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,212,326

b. Issue Date of Patent
May 18, 1993

c. Expiration Date of Patent
January 29, 2008

d. Name of Patent Owner
Abbott Laboratories

Address (of Patent Owner)
100 Abbott Park Road, 377/AP6A-1

City/State
Abbott Park, Illinois

ZIP Code
60064-6008

FAX Number (if available)
847-938-2623

Telephone Number
847-937-6364

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. The patent claims, among others, the form of the drug substance in the drug product that is the subject of the approved NDA as well as the present NDA supplement and is submitted for listing on that basis, so no additional testing is required.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed September 5, 2007
---	----------------------------------



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Robert DeBerardine	
Address Abbott Laboratories 100 Abbott Park Road, 377/AP6A-1	City/State Abbott Park, Illinois
ZIP Code 60064-6008	Telephone Number 847-937-6364
FAX Number (if available) 847-938-2623	E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

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First Section

Complete all items in this section.

I. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
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2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

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3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-168

NAME OF APPLICANT / NDA HOLDER

Abbott Laboratories

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Depakote® ER

ACTIVE INGREDIENT(S)

Divalproex sodium

STRENGTH(S)

500 mg

DOSAGE FORM

Tablet, Extended Release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,419,953

b. Issue Date of Patent

July 16, 2002

c. Expiration Date of Patent

December 18, 2018

d. Name of Patent Owner

Abbott Laboratories

Address (of Patent Owner)

100 Abbott Park Road, 377/AP6A-1

City/State

Abbott Park, Illinois

ZIP Code

60064-6008

FAX Number (if available)

847-938-2623

Telephone Number

847-937-6364

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Claims 14, 15 and 16 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Claims 14, 15 and 16: Treatment of epilepsy in accordance with proposed labeling, including the "Indications and Usage" and "Dosage and Administration" sections

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

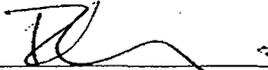
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
September 5, 2007



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Robert DeBerardine

Address

Abbott Laboratories
100 Abbott Park Road, 377/AP6A-1

City/State

Abbott Park, Illinois

ZIP Code

60064-6008

Telephone Number

847-937-6364

FAX Number (if available)

847-938-2623

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER

21-168

NAME OF APPLICANT / NDA HOLDER

Abbott Laboratories

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Depakote[®] ER

ACTIVE INGREDIENT(S)

Divalproex sodium

STRENGTH(S)

250 mg and 500 mg

DOSAGE FORM

Tablet, Extended Release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,511,678

b. Issue Date of Patent

January 28, 2003

c. Expiration Date of Patent

December 18, 2018

d. Name of Patent Owner

Abbott Laboratories

Address (of Patent Owner)

100 Abbott Park Road, 377/AP6A-1

City/State

Abbott Park, Illinois

ZIP Code

60064-6008

FAX Number (if available)

847-938-2623

Telephone Number

847-937-6364

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)



Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Claims 7 and 8 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Claims 7 and 8: Treatment of migraine in accordance with proposed labeling, including the "Indications and Usage" and "Dosage and Administration" sections

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

EXCLUSIVITY SUMMARY

NDA # 22-267

SUPPL # [Type 6 NDA]

HFD # 130, DPP

Trade Name Depakote ER

Generic Name divalproex sodium extended-release tablets

Applicant Name Abbott Laboratories

Approval Date, If Known PDUFA Goal Date is March 24, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8
(b)(1) Type 6 NDA in lieu of a (b)(1) SE5 pediatric supplement.

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:

The submission has been made to fulfill PREA requirements and meet the terms of a Pediatric Written Request for Exclusivity. Pediatric Exclusivity has been granted. The efficacy study in the pediatric bipolar indication is a failed study. However, the labeling is required to describe the study, additional safety information has been added, and the labeling is also being reformatted to meet PLR requirements.

d) Did the applicant request exclusivity?

They have requested Pediatric Exclusivity Only 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 the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes.

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

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 22-267

Type 6 NDA

Exclusivity Summary

NDA# 18723	Depakote (divalproex sodium)
NDA# 19680	Depakote, simple and complex absence seizures
NDA# 19794	Depakote CP
NDA# 20320	Depakote Tablets
NDA # 20782	Depakote ER
NDA# 21168	Depakote ER

2. Combination product.

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 8.

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 NO

A clinical investigation was required to meet the terms of PREA and the Written Request, to generate safety data which is being included in the labeling. Information on the studies that were conducted will also be included in the labeling although no claim can be approved because the studies failed. The approval, in this case, is approval of revisions to labeling and of labeling format change, not of a new efficacy claim.

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 8:

(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:

Study M01-342 : note: *for this indication only ONE double blind, placebo controlled study was required.*

Study M02-555 : note: this is an open label safety study of six months' duration, including 66 patients, required to meet the terms of the Written Request and of PREA.

Study M02-540 : note: this is a second open label safety study also of six months' duration, including 226 patients, required to meet the terms of the Written Request and of PREA.

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

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:

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 investigation, identify the NDA in which a similar investigation was relied on:

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 M01-342 : note: *for this indication only ONE double blind, placebo controlled study was required.*

Investigation #2 = Study M02-555 : note: this is an open label safety study of six months' duration, including 66 patients, required to meet the terms of the Written Request and of PREA.

Investigation #3 = Study M02-540 : note: this is a second open label safety study also of six months' duration, including 226 patients, required to meet the terms of the Written Request and of PREA.

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 Study M02-540 : **note: for this indication only one study was required.**

IND #30673 YES ! NO
! Explain:

Investigation #2

IND # 30673 YES ! NO
! Explain:

Investigation #3

IND # 30673 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?

NOT APPLICABLE

Investigation #1

YES ! NO
Explain: ! Explain:

Investigation #2

YES ! NO
Explain: ! 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:

Name of person completing form: Doris J. Bates, Ph.D.
Title: Regulatory Health Project Manager
Date: March 5, 2008

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Doris Bates
3/24/2008 11:54:20 AM

Thomas Laughren
3/24/2008 12:07:40 PM



Notice of Claim for Exclusivity: 6-Month Pediatric Exclusivity

As defined by FDA Guidance for Industry "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act," Abbott Laboratories herein claims 6-months of Pediatric Exclusivity which would attach to each patent listed in force and under "Patent Information" and attach to existing exclusivity listed under "Hatch-Waxman Exclusivity" (see Orange Book). FDA issued a Written Request (WR) to Abbott Laboratories on August 9, 2002 and reissued the Written Request on January 31, 2006. This supplemental New Drug Application (sNDA) contains final clinical study reports for clinical investigations:

M01-342: A Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Depakote ER for the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents

M02-555: An Open-Label Long-Term Study to Evaluate the Safety of Depakote Extended Release Tablets in the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents

M03-647: An Open-Label Study to Evaluate the Safety of Depakote® ER in the Treatment of Mania Associated with Bipolar I Disorder in Children and Adolescents



M02-488: The Safety and Efficacy of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents

M02-554: The Safety of Divalproex Sodium Extended Release Tablets in Migraine Prophylaxis: An Open-Label Extension Study in Adolescents

M03-648: Divalproex Sodium Extended-Release Tablets for Migraine Prophylaxis in Adolescents: An Open-Label, Long-Term Safety Study

M04-714: An Open-Label Multicenter Study of the Long-Term Safety of Depakote® Sprinkle Capsules in the Treatment of Partial Seizures in Children

In addition, the following are provided in this sNDA per the Written Request:

- Pharmacokinetic literature review with calculated age-appropriate dosing regimens for pediatric subjects aged 3-10 years old as described in the Written Request.
- A report on the spontaneous US reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy patients 3-10 years of age and 11-17 years of age during a prescribed period of time. These rates are also provided after stratifying by VPA monotherapy and VPA use in combination with other antiepileptic medications.



Depakote ER (divalproex sodium extended-release) ABT-711
Notice of Claimed Exclusivity: 6-Month Pediatric Exclusivity

These studies were conducted in compliance to the FDA WR, and as defined by the Section 505A of the Federal, Food, Drug and Cosmetic Act. Abbott Laboratories herein is eligible for and claims 6-months Pediatric Exclusivity as defined above.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-267 Supplement Type (e.g. SE5): Type 6 NDA Supplement Number: _____

Stamp Date: September 24, 2007 PDUFA Goal Date: March 24, 2008

HFD 130 Trade and generic names/dosage form: Depakote ER (divalproex sodium) extended-release tablets

Applicant: Abbott Laboratories Therapeutic Class: Antimanic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements or Type 6 NDAs only): Migraine prophylaxis, Epilepsy (adult and pediatric), monotherapy in the treatment of acute manic or mixed episodes associated with Bipolar I Disorder, with or without psychotic features (adult).

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: bipolar disorder in pediatric patients ages 10 to 17

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 9 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: disease/condition not known to exist in this age group

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 (fill in applicable criteria below):

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): _____

If studies are complete, 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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 10 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments: Note that the efficacy study performed, while meeting the terms of the Pediatric Written Request as issued August 9, 2002 and reissued January 31, 2006, and also meeting the requirements of the PREA Phase 4 Commitment for NDA 21-168 S-012 [approval letter issued December 6, 2005], *failed to demonstrate efficacy of Depakote ER in this population and this indication.*

The labeling has been revised to describe the study performed and incorporate new safety information gleaned. The action to be taken on this application is an approval for the labeling only, with clear stipulation that the requirements of the PREA commitment have been met.

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

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Doris Bates

3/24/2008 11:59:40 AM

Type 6 NDA. Submission cross references 21-168 S-015.

PEDIATRIC PAGE

NDA/BLA #: 21-168 Supplement Type (e.g. SE5): SE1 Supplement Number: 012

Stamp Date: October 26, 2004 Action Date: Resubmission Class I Goal Date December 11, 2005

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

Applicant: Abbott Laboratories Therapeutic Class: 6S

Indication(s) previously approved: Migraine prophylaxis, Epilepsy (adult and pediatric)

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

Number of indications for this application(s): 1

Indication #1: monotherapy in the treatment of acute manic or mixed episodes associated with Bipolar I Disorder, with or without psychotic features

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:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 10 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: disease/condition not known to exist in this age group

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:

Min _____ kg _____ mo. _____ yr. 10 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 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): October 7, 2007

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 21-168 / S-012
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Doris Bates

12/1/2005 03:43:28 PM

See AP letter for date of supplement approval.



Depakote ER (divalproex sodium extended-release) ABT-711

Debarment Certification

Depakote Products (ABT-711)

DEBARMENT CERTIFICATION

Abbott Laboratories hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Julie Fugate 17 August 2007

Julie Fugate

Date

Clinical Research Manager

GPRD Neuroscience /Anesthesia Development

Abbott Laboratories

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6157

September 21, 2007

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

Subject: USER FEE I.D. NUMBER PD3007682

Dear Sir or Madam:

Enclosed is a check in the amount of \$448,100 to cover the user fee payment for the following application:

Product Name: Depakote ER capsules
Generic Name: divalproex sodium
Indications for use: bipolar disorder - mania
Type of Submission: Supplement with clinical data
NDA Number: 22-267
Name of Sponsor: Abbott Laboratories
Address: D-PA76, Building AP30-1NE
200 Abbott Park Road
Abbott Park, IL 60064-6157
Contact Person: Steven Hoff, Ph.D.
Telephone Number: (847)935-6244

Sincerely,



Steven F. Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs

Enclosures: Abbott Check Number – 00048449 \$448,100
User Fee Cover Sheet

Cc: Colin Walters, R404, AP34
Ed Roles, AP6C-1

Abbott

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS ABBOTT LABORATORIES Mary Konkowski 200 Abbott Park Road RA76, AP30-1E Abbott Park IL 60064-6157 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-267			
2. TELEPHONE NUMBER 847-938-3063		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
3. PRODUCT NAME Depakote (divalproex sodium)		6. USER FEE I.D. NUMBER PD3007682			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
<p>OMB Statement Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td> <td>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.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE MANAGER - GLOBAL PHARMACEUTICAL REGULATORY AFFAIRS DATE 20 Sept 2007			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$448,100.00					
Form FDA 3397 (03/07)					

Close Print Cover sheet

Griffis, Melina

From: Griffis, Melina
Sent: Monday, December 17, 2007 10:26 AM
To: 'Steven F Hoff'
Subject: Pediatric Exclusivity Notification

Pediatric Exclusivity has been granted for studies conducted on valproate, effective December 14, 2007, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act 2007 (BPCA 2007). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the "Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act." <http://www.fda.gov/cder/guidance/2891fnl.pdf>

In addition, the FDA Amendments Act of 2007, Title V: BPCA of 2007, enacted on September 27, 2007, mandates that all adverse event reports must be referred to the Office of Pediatric Therapeutics one year after a labeling change is approved for applications and supplements submitted under subsection (i). The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

For most products, the presentation at the PAC meeting will be one of the following:

- 1) "Abbreviated" presentation: brief comments presented to the PAC concerning the lack of any safety signal.
- 2) "Standard" presentation: a review of Adverse Event Reporting Systems (AERS) data, use data, the exclusivity trials with a focus on the safety reporting, and any additional information thought to be pertinent to the review and discussion.
- 3) "In-depth" presentation: "standard" presentation noted above plus safety issues identified as requiring a more in-depth discussion and review. This may involve external experts and presentations and discussion by Office of Surveillance and Epidemiology and the review division staff.

The type of presentation will depend on the adverse event data and other issues under review at the time. The Agency will not determine the type of presentation until after we have reviewed the relevant data and information. Irrespective of the type of presentation, the PAC will receive a briefing package which includes the Adverse Event review, product use review, the exclusivity review summaries and the current labeling.

If you have questions relating to the Pediatric Advisory Committee, please call Ann Myers, R.Ph., in the Office of Pediatric Therapeutics at 301-827-9379.

Melina N. Griffis, R.Ph., CDR-USPHS
Senior Regulatory Project Manager
Division of Neurology Products, CDER, FDA
10903 New Hampshire Ave, Bldg 22, Rm 4355
Silver Spring, MD 20993-0002

Office- 301-796-1078 Fax- 301-796-9842
Email- melina.griffis@fda.hhs.gov

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/s/

Melina Griffis
12/18/2007 10:03:58 AM
CSO

orig

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 01/03/06 (previous versions dated 8/9/02, 5/7/04 & 12/21/05 were superseded or incorporated into the 1/3/06 final WR)
 Application Written Request was made to: NDA/IND#: NDAs 18-723, 19-680, 20-320, 20-593, 20-782, 21-168 and IND 32,321
 Timeframe Noted in Written Request for Submission of Studies : 10/7/2007
 NDA# 19-680/S-024, 21-168/S-015, NDA 22-267_ Choose one: SE5 & Type 6 NDA
 Sponsor Abbott
 Generic Name divalproex sodium Trade Name: Depakote ER and Depakote Sprinkle Capsules
 Strength: 125mg (Sprinkles) & 250mg or 500mg (ER) Dosage Form/Route: ER & Sprinkle Capsules/Oral
 Date of Submission of Reports of Studies 9/24/07
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/23/07

Was a formal Written Request made for the pediatric studies submitted?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>
Were the studies submitted after the Written Request?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>
Was the timeframe noted in the Written Request for submission of studies met?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>
If there was a written agreement, were the studies conducted according to the written agreement? <i>OR</i> If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>
Did the studies fairly respond to the Written Request?	Y <input checked="" type="checkbox"/> X <input type="checkbox"/>	N <input type="checkbox"/>

SIGNED [Signature] (DPP)

DATE 11-30-07

SIGNED [Signature] (DNP)

DATE 12-3-07

(Reviewing Medical Officers)

SIGNED [Signature] (DPP)

DATE 11-30-07

SIGNED [Signature] (DNP)

DATE 12/3/07

(Division Directors)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

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/s/

John Jenkins

12/14/2007 09:51:32 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-267 Supplement # Type 6 NDA Efficacy Supplement Type SE-

Proprietary Name: Depakote ER
Established Name: divalproex sodium, Tablet, Extended Release, for oral use
Strengths: 250 mg and 500 mg

Applicant: Abbott Laboratories
Agent for Applicant (if applicable): Not Applicable

Date of Application: 24 September 2007
Date of Receipt: 24 September 2007
Date clock started after UN: not applicable
Date of Filing Meeting: 7 November 2007
Filing Date: 23 November 2007

Action Goal Date (optional): User Fee Goal Date: 24 March 2008
Indication(s) requested: No claim was requested by the applicant. This Type 6 NDA included reports from one adequate and well controlled study of Depakote ER in the treatment of adolescent mania in association with bipolar disorder, plus safety data for this indication.

Type of Original NDA: (b)(1) X (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

This is a Type 6 NDA in lieu of a supplement because the indication is in HFD-130 but the NDA is in HFD-120.

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P X
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 6 P
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's

proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Note all exclusivity information refers to NDA 21-168. 21-168 has exclusivity under the bipolar indication until December 6, 2008.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).
 1. This application is a paper NDA YES NO
 2. This application is an eNDA or combined paper + eNDA YES NO
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats
- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, Years NO X

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. Comment: Pediatric Exclusivity is requested and the terms of the WR are met. However, the efficacy study failed, and therefore the applicant is not requesting a claim per se or any exclusivity other than pediatric exclusivity under the WR.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES X NO

If yes, contact PMHS in the OND-IO Done.

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 18872, 30673. , 36945, 58683.

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.

b(4)

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
Comment: See sponsor's chronology of correspondence. Email correspondence sent by Abbott to HFD-120, on 26FEB07, stood in lieu of a presubmission meeting with 120. 130 was not included in this correspondence. 120 replied to Abbott on 16MAY07.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.
Comment: See sponsor's chronology of correspondence. SPA request was submitted 06NOV02 and responded to on 11DEC02; Abbott then requested revision to WR on 25MAR03 and 27OCT04. See Written Requests for final FDA position.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO X

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: PLR was submitted October 31, 2007.

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? Not applicable
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7 November 2007

NDA #: 22-267

DRUG NAMES: Depakote ER (divalproex sodium) extended release tablets

APPLICANT: Abbott Laboratories

BACKGROUND: This is a Type 6 NDA submitted as an SE5 to HFD-120 to meet the terms of PREA Phase 4 commitment for adult bipolar, 21-168 SE1-012, approved December 6, 2005, and also to meet the terms of the Pediatric Written Request, issued August 9, 2002, revised May 7, 2004 and December 21, 2005, and reissued January 31, 2006.

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Attendees

Medical:

Katz, Laughren, Mathis, Bastings, Feeney,
Sheridan, Ritter

Secondary Medical:

Statistical:

Yang

Pharmacology:

not applicable

Statistical Pharmacology:

not applicable

Chemistry:

failed study; not applicable

Environmental Assessment (if needed):

not applicable

Biopharmaceutical:

Uppoor

Microbiology, sterility:

not applicable

Microbiology, clinical (for antimicrobial products only):

not applicable

DSI:

not applicable

OPS:

not applicable

Regulatory Project Management:

Griffis, Bates

Other Consults:

not applicable

SYNOPSIS: This meeting was scheduled and managed by HFD-120, to discuss three concurrently submitted supplements responding to the above referenced WR. HFD-130 will review and act upon the submission for bipolar mania, Type 6 NDA 22-267. All three submissions were considered fileable; however, the applicant was required to submit PLR formatted labeling ASAP. There were no clinical efficacy studies submitted for either neurological indication, the clinical pharmacology portion of the submission is based on published literature, and the controlled study submitted to satisfy PREA for NDA 21-168 S-012 and the PWR for adolescent bipolar disorder failed.

The submission appears to meet the terms of the WR. A PEB meeting will be held. The submission also fulfills the postmarketing commitment and results in revised labeling to describe pediatric studies and update relevant safety information. Therefore, *the most likely action to be taken will be approval of labeling, with clear statements in the AP letter that the indications themselves are not approved, and in fact, the applicant has sought no claims.*

See electronic signature page: this checklist with meeting synopsis is prepared by Dr. Bates for HFD-130.

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/s/

Doris Bates

3/24/2008 12:10:44 PM

Filing minutes and CSO checklist for NDA 22-267

Table of Contents
NDA 22-267
DEPAKOTE ER® (divalproex sodium) Extended Release Tablets
Type 6 NDA: Pediatric Bipolar Disorder
APPROVAL [note caveats]
DUE DATE: March 24, 2008

Approval [note caveats]: Action Package:

Table of Contents & Action Package Checklist: Front of File

1. Action Letter & Labeling
 - AP Letter
 - Final Agreed Upon Labeling [PLR]
 - Applicant Proposed Labeling
 - PLR Labeling Review Not Required: Approved PLR Label Used as Base Document
2. Regulatory Information
 - Patent Information [Orange Book]
 - Patent Certification and *Non-Pediatric* Exclusivity Checklist
 - Debarment Certification and User Fee Information
3. Pediatric Page & *Pediatric* Exclusivity
 - Pediatric Page
 - AP letter for 21-168 S-012 listing PREA Phase 4 commitment
 - Pediatric Page for 21-168 S-012
 - Written Request Letters
 - Template for PEB re Written Request
 - Exclusivity Notification and Checklist
4. Administrative Memoranda
 - Division Director Memo
 - Clinical Team Leader Memo
5. Consult Reviews
 - DSI Information: No Inspection Required
 - Statistical Review Not Required; Efficacy Study Failed, No Claim Sought; See Caveats.
 - Clinical Pharmacology Review: Cross Reference 21-168 S-015 Review, Included
 - Nonclinical Pharmacology: Not Required
 - Chemistry: Memo, Cross-Reference 21-168 S-015 Review, Included.
6. Clinical Review
 - Safety Review (see Clinical Review)
7. Correspondence, Minutes of Meetings, Submission History
 - Correspondence Applicant to FDA
 - Correspondence FDA to Applicant
 - Filing Review PM Checklist and Filing Meeting Minutes
 - PeRC Meeting, March 12, 2008
 - EDR History
 - DSS History

CAVEATS: This submission provides reports for one failed efficacy study and one open label safety study conducted to meet the requirements of PREA and the Pediatric WR. Exclusivity has been granted. The labeling is required to describe the studies and has been submitted in PLR format. Therefore, labeling is being approved, but no pediatric efficacy claim will be approved. The action letter is phrased accordingly.

NDA 22-267
ACTION PACKAGE CHECKLIST -- TYPE 6 NDA

Application Information		
NDA 22-267	Efficacy Supplement Type <i>type 6 NDA</i>	Supplement Number not applicable
Drug: Depakote ER (divalproex sodium extended release tablets)		Applicant: Abbott Laboratories
RPM: Bates	HFD-130	Phone # 301 796 1040
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		<i>Pediatric (WR and PREA)</i>
❖ User Fee Goal Dates		March 24, 2008
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number PD3007682
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP) <i>NOT APPLICABLE</i>		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted for patents that claim		<input checked="" type="checkbox"/> Verified

the drug for which approval is sought.	
❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Yes, through Dec. 6, 2008. Also note that pediatric exclusivity has been granted and is valid through June 6, 2009.
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	See Table of Contents
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(✓) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	AE, 18-AUG-2005
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H (✓) A new claim is not being approved. Therefore, no advertising is requested.
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(✓) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(✓) TBD by Press Office () None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	✓
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	✓
<ul style="list-style-type: none"> Original applicant-proposed labeling 	✓
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	✓ See Clinical and Clinical Pharmacology reviews
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	NOT APPLICABLE
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) Applicant proposed Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments Documentation of discussions and/or agreements relating to post-marketing commitments 	See AP letter for all information
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	not applicable

<ul style="list-style-type: none"> • Pre-NDA meeting (indicate date) 	Not applicable
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (indicate date; approvals only) 	Not applicable
<ul style="list-style-type: none"> • Other 	Filing meeting minutes included
❖ Advisory Committee Meeting	NOT APPLICABLE
<ul style="list-style-type: none"> • Date of Meeting 	
<ul style="list-style-type: none"> • 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	✓
Clinical Information	
❖ Clinical review(s)	✓
❖ Microbiology (efficacy) review(s)	NA
❖ Safety Update review(s)	NA
❖ Risk Management Plan review(s)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Demographic Worksheet (<i>NME approvals only</i>)	NA
❖ Statistical review(s)	NA: efficacy study failed; AP is for labeling revisions and format change only.
❖ Biopharmaceutical review(s)	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	NA
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> • Clinical studies 	NA: efficacy study failed.
<ul style="list-style-type: none"> • Bioequivalence studies 	NA
CMC Information	
❖ CMC review(s)	✓: See Memo
❖ Environmental Assessment	
<ul style="list-style-type: none"> • Categorical Exclusion 	✓: See Memo
<ul style="list-style-type: none"> • Review & FONSI 	
<ul style="list-style-type: none"> • Review & Environmental Impact Statement 	
❖ Facilities inspection (provide EER report)	NOT APPLICABLE Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	NOT APPLICABLE () Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews	NA
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	NA
❖ CAC/ECAC report	NA

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/s/

Doris Bates
3/24/2008 12:02:18 PM

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6157

December 12, 2007

Tom Laughren, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Amendale Road
Beltsville, MD 20705-1266

**Re: Depakote ER (divalproex sodium) extended release tablets
NDA 22-267**

Subject: Response to FDA information requests: Clinical

Dear Dr. Laughren:

The sponsor, Abbott Laboratories, submits the following information in support of this Prior Approval supplement under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505 and 21 CFR 201.58 for Depakote ER tablets, Type 6 NDA 22-267.

In response to your filing letter dated November 19, 2007, Abbott is providing the following responses to your information requests. Please note that the information for requests #1 and #2 were provided to the Agency in two emails to Doris Bates, Regulatory Project Manager, on December 7, 2007.

1) We request that you submit all reports of pediatric foreign regulatory actions and pediatric foreign post marketing surveillance reports.

a) *Pediatric foreign regulatory actions:* At this time the Abbott Ex-US affiliates report that only Venezuela has approved Depakote for pediatric use for the mania indication. We are not aware of any additional regulatory activity.

b) *Pediatric foreign postmarketing surveillance reports:* Please find the requested information in the attached section item 8, which contains all of the foreign postmarketing surveillance reports. This is a very large file, containing 39 mb and 5510 pages of information.

Abbott

NDA 22-267

Depakote ER (extended release) tablets

December 12, 2007

2) We also request that you perform and submit a demographic analysis as soon as possible for the common adverse events the occurred in the placebo controlled study.

The requested demographic analysis for the common adverse events occurring in study M01-342 is provided in the attached section item 8.

3) We are not able to use the JMP datasets to analyze adverse events, lab results or other data collected by treatment, as there does not appear to be a column to specify treatment assignment (placebo or Depakote ER). We have located the subject ID and allocated treatment data in a separate dataset, but it appears that the treatment allocation information was not integrated into the other data sets. Please update the JMP datasets to include a column for both subject ID and treatment allocation to facilitate comparison of the two groups on the various submitted data.

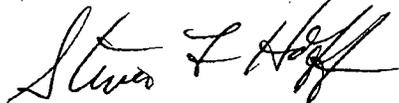
We have revised the JMP datasets per your request. The datasets are located in the attached section item 11.

This submission is being provided electronically. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations, IT2 (January 1999), and Providing Regulatory Submissions to in Electronic Format - NDAs, IT3 (January 1999). The submission comprises less than 45 megabytes of space. This information was checked for viruses using McAfee VirusScan Enterprise 8.0i and determined to be virus free.

Please contact me at the numbers below if you have any questions or require additional information.

Sincerely,

ABBOTT LABORATORIES



Steven F. Hoff, Ph.D.

Associate Director

Global Pharmaceutical Regulatory Affairs

Phone: 847-935-6244

FAX: 847-887-8251

Attachment:



**NDA FILING COMMUNICATION
FILING ISSUES IDENTIFIED (CLINICAL)**

NDA 22-267

Abbott Laboratories
Attention: Steven F. Hoff, R. Ph., Ph.D.
Associate Director
Global Pharmaceutical Regulatory Affairs
PA76, Building AP30-1E
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Dear Dr. Hoff:

Please refer to your new drug application submitted and received September 24, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDC Act) for Depakote ER (divalproex sodium extended-release tablets) 250 mg and 500 mg.

This Type 6 pediatric NDA submission supports safety labeling changes to incorporate pediatric use information for the indication of bipolar disorder - mania. The final study reports included within the submission are provided in support of your claim of Pediatric Exclusivity for Depakote, as described by the FDC Act, section 505A.

The filing date for this application is November 23, 2007; as you were informed by Melina Griffis (Division of Neurology Products) on November 7, 2007, we have completed our filing review and have determined that your application is sufficiently complete to permit substantive review. Therefore, this application will be filed under section 505(b) of the Act in accordance with 21 CFR 314.101(a). As it is a Pediatric Exclusivity submission, the user fee goal date is March 24, 2008.

At this time we have identified the following review issues, and request that you submit information to address them:

CLINICAL

- 1) We request that you submit all reports of pediatric foreign regulatory actions and pediatric foreign post marketing surveillance reports.
- 2) We also request that you perform and submit a demographic analysis as soon as possible for the common adverse events the occurred in the placebo controlled study.
- 3) We are not able to use the JMP datasets to analyze adverse events, lab results or other data collected by treatment, as there does not appear to be a column to specify treatment assignment

(placebo or Depakote ER). We have located the subject ID and allocated treatment data in a separate dataset, but it appears that the treatment allocation information was not integrated into the other data sets. Please update the JMP datasets to include a column for both subject ID and treatment allocation to facilitate comparison of the two groups on the various submitted data.

We are providing the above comments to give you early notice of review issues identified at this time. The filing review is only a preliminary evaluation of the application and should not be considered indicative of all deficiencies that may be identified during our review. Therefore, issues may be added, deleted, expanded upon, or modified as we continue our substantive review of the application.

Please respond to the above requests for additional information at this time. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260.

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

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/s/

Thomas Laughren
11/19/2007 12:42:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 19-680/S-024
NDA 21-168/S-015

Abbott Laboratories
Attention: Steven Hoff, Ph.D.
200 Abbott Park Road, RA-76, AP30-1E
Abbott Park, Illinois 60064-6157

Dear Dr. Hoff:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakote Tablets and Depakote ER Tablets.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on November 23, 2007 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Melina Griffis, R.Ph., Sr. Regulatory Project Manager, at (301) 796-1078.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
11/15/2007 07:56:44 AM

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6157

November 14, 2007

Tom Laughren, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Amendale Road
Beltsville, MD 20705-1266

**Re: Depakote ER (divalproex sodium) extended release tablets
NDA 22-267**

Subject: Response to FDA information requests: Clinical, CMC

Dear Dr. Laughren:

The sponsor, Abbott Laboratories, submits the following information in support of this Prior Approval supplement under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505 and 21 CFR 201.58 for Depakote ER tablets, Type 6 NDA 22-267. This submission is cross-referenced to NDA 21-168, S-015 dated September 24, 2007.

CLINICAL

Please refer to your email received on October 29, 2007, in which your clinical reviewer requested information for the following questions related to bipolar disorder only.

1. Please provide a copy (e-version if it's easier) of the WASH-U-KSADS as a review aid for the clinical reviewer. In particular, the reviewer is interested in the 'expanded mania' supplement section and how the WASH-U-KSADS defines a 'manic' episode.

Please find an e-copy of the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) scoring manual (definition of a Manic Episode – See page 14) and the Section 1 of the WASH-U-KSADS (Expanded mania supplement section – See pages 72 - 95). Also note that an electronic copy of the scoring manual was provided to you by email on November 1, 2007.

The definition of a Manic Episode by the WASH-U-KSADS is based on the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) Criteria for Manic Episode. The table below highlights (in blue) any differences between the DSM-IV-TR and the WASH-U-KSADS Criteria for Manic Episode. Differences between the two sets or criteria reflect the fact that children are developmentally incapable of some manifestations of bipolar symptoms described in adults (Geller et. al, 2002a).

DSM-IV-TR Criteria
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to significant degree: <ul style="list-style-type: none">(1) inflated self-esteem or grandiosity(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)(3) more talkative than usual or pressure to keep talking(4) flight of ideas or subjective experience that thoughts are racing(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a Mixed Episode
D. The mood disturbance is sufficiently severe to cause marked impairment in



b(4)

occupational functioning or in usual social activities or relationships with others. Or there are psychotic features

E. The symptoms are not due to the direct physiological effect of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism)

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

b(4)

2. Please explain how you have defined a 'Manic' episode (i.e. please indicate whether you used the "narrow" NIMH phenotype, where patients must have elation, grandiosity AND discrete episodes lasting at least 1 week, or the "broad" phenotype of severe irritability and rapid mood swings).

As per study protocols (M01-342, M02-555, and M03-647), subjects had a current clinical diagnosis of bipolar I disorder, manic or mixed episode, according to the DSM-IV-TR criteria using the WASH-U-KSADS. The WASH-U-KSADS interview was conducted by a qualified mental health professional during the Screening Period and a qualified (e.g., board eligible or board certified) child psychiatrist confirmed the diagnosis of bipolar I disorder, manic or mixed episode prior to randomization. Dr. Barbara Geller, one of the developers of the WASH-U-KSADS, trained raters during the M01-342 investigators meeting.

NIMH mania phenotypes were not specifically used in the Abbott Depakote Mania studies. However, the criteria that were used in these protocols, in particular the DSM-IV-TR criteria for bipolar I disorder, manic or mixed episode using the WASH-U-KSADS, appear to be generally similar to the NIMH "narrow" phenotype (Leibenluft, 2003, see Appendix B). The only difference between the DSM-IV-TR and the "narrow" phenotype criteria is in criterion A where the "narrow" phenotype includes "grandiosity" in addition to elevated/expansive mood while the DSM-IV describes elevated/expansive or irritable mood. In contrast, the "broad" phenotype lacks the hallmark symptoms of mania (elevated/expansive mood or grandiosity) but shares the symptoms of severe irritability and hyperarousal (Leibenluft, 2003, see Attachment A on this letter).

References:

Geller B et al (2002): Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. *J Child & Adolescent Psychopharm* 12 (1): 3-9

Leibenluft et al (2003): Defining clinical phenotypes of juvenile mania. Am J Psychiatry 160 (3): 430-437

Other relevant references:

Geller B et al (2001): Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) Mania and Rapid Cycling Sections. J Am Acad Child Adoles Psychiatry 40 (4): 450-455

Geller B and Tillman (2005): Prepubertal and early adolescent bipolar I disorder: review of diagnostic validation by Robins and Guze criteria (2005): J Clin Psychiatry 66 (suppl 7): 21-28

Ghaemi and Martin (2007): Defining the Boundaries of Childhood Bipolar Disorder. Am J Psychiatry 164 (2): 185-188

Copies of the above references are provided in Section 8 – Clinical.

CMC

Please refer to your email received on November 1, 2007, in which your chemistry reviewer requested a specific categorical exclusion request or an environmental assessment, which was specific to NDA 22-267. A copy of the categorical exclusion request for NDA 22-267 is provided in Section 20 - Other. A copy was also provided to the Agency by email on November 1, 2007.

This submission is being provided electronically. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations, IT2 (January 1999), and Providing Regulatory Submissions to in Electronic Format - NDAs, IT3 (January 1999). The submission comprises less than 10 megabytes of space. This information was checked for viruses using McAfee VirusScan Enterprise 8.0i and determined to be virus free.

Please contact me at the numbers below if you have any questions or require additional information.

Sincerely,

ABBOTT LABORATORIES



Steven F. Hoff, Ph.D.
Associate Director
Global Pharmaceutical Regulatory Affairs

Phone: 847-935-6244
FAX: 847-887-8251

Attachment:

Attachment A

Criteria for the Narrow Phenotype of Juvenile Mania: Mania, With Full-Duration Episodes and Hallmark Symptoms

Modification to the DSM-IV criteria for manic episode

The child must exhibit either elevated/expansive mood or grandiosity, while also meeting the other DSM-IV criteria for a manic episode.

Guidelines for applying the DSM-IV criteria

Episodes must meet the full duration criteria (i.e., ≥ 7 days for mania and ≥ 4 days for hypomania) and be demarcated by switches from other mood states (depression, mixed state, euthymia).

Episodes are characterized by a change from baseline in the patient's mood (DSM-IV criterion A) and, simultaneously, by the presence of the associated symptoms (DSM-IV criterion B). For example, the distractibility of a child with ADHD would count toward a diagnosis of mania only if his/her distractibility worsened at the same time that he/she experienced mood elevation.

Decreased need for sleep should be distinguished from insomnia (i.e., nonspecific difficulty sleeping, which is associated with fatigue).

Poor judgment per se is not a diagnostic criterion for mania; the poor judgment must occur in the context of "increased goal-directed activity" or "excessive involvement in pleasurable activities that have a high potential for painful consequences."

Note: The Narrow Phenotype modification to the DSM-IV criterion A consists in including "grandiosity" in addition to elevated/expansive mood. The DSM-IV criterion A describes elevated, expansive or irritable mood.

Criteria for the Broad Phenotype of Juvenile Mania: Severe Mood and Behavioral Dysregulation

Inclusion criteria

Age 7–17 years, with the onset of symptoms before age 12.

Abnormal mood (specifically, anger or sadness) present at least half of the day most days and of sufficient severity to be noticeable by people in the child's environment (e.g., parents, teachers, peers).

Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness.

Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week for the past 4 weeks.

The symptoms noted in the previous three items are currently present and have been present for at least 12 months without any symptom-free periods exceeding 2 months in duration.

The symptoms are severe in at least in one setting (e.g., violent outbursts or assaultiveness at home, at school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.

Exclusion criteria

The individual exhibits any of these cardinal bipolar symptoms: elevated or expansive mood, grandiosity or inflated self-esteem, episodically decreased need for sleep.

The symptoms occur in distinct periods lasting more than 4 days.

The individual meets the criteria for schizophrenia, schizophreniform disorder, schizoaffective illness, pervasive developmental disorder, or posttraumatic stress disorder.

The individual has met the criteria for substance use disorder in the past 3 months.
IQ <80.

The symptoms are due to the direct physiological effects of a drug of abuse or to a general medical or neurological condition.

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60084-0157

October 31, 2007

Tom Laughren, M. D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Amendale Road
Beltsville, MD 20705-1266

**Re: Depakote ER (divalproex sodium) extended release tablets
NDA 22-267**

Subject: Requested Depakote PLR Labeling and WAIVER REQUEST

Dear Dr. Laughren:

The sponsor, Abbott Laboratories, submits the following information in support of this Prior Approval supplement under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505 and 21 CFR 201.58 for Depakote ER tablets, NDA 22-267. At the request of the Division of Neurology Products, Abbott is providing proposed labeling in the PLR format for Depakote ER tablets.

Full documentation in support of this submission is cross-referenced to the sNDA to Depakote ER tablets, NDA 21-168, submitted on October 31, 2007 to the Division of Neurology Products. A copy of the cover letter to NDA 21-168 is attached.

Please contact me at the numbers below if you have any questions or require additional information.

Sincerely,

ABBOTT LABORATORIES



Steven F. Hoff, Ph.D.
Associate Director
Global Pharmaceutical Regulatory Affairs
Phone: 847-935-6244
FAX: 847-887-8251

Abbott

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6157

October 31, 2007

Russell Katz, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Re: NDA 19-680 Depakote® Sprinkle Capsules
NDA 21-168 Depakote® ER**

Subject: Requested Depakote PLR Labeling and WAIVER REQUEST

Dear Dr. Katz:

On September 24, 2007, Abbott Laboratories made a submission to NDAs 21-168, 19-680 and 22-267 requesting a determination of pediatric exclusivity for Depakote ER tablets and Depakote Sprinkle capsules. Cross-reference is made to our submission of NDA 22-267 for Depakote ER tablets to the Division of Psychiatry Products. On October 12, 2007, Senior Regulatory Project Manager, Melina Griffis informed Abbott that a potential filing issue had been identified, because labeling had not been submitted in PLR format. On October 17, 2007, Melina Griffis followed up with Abbott to confirm the requirement for PLR labeling for both Depakote ER tablets (NDA 21-168, 22-267) and Depakote Sprinkle capsules (NDA 19-680), and the labeling would need to be at FDA no later than November 7, 2007.

This submission provides the required labeling for Depakote ER tablets and Depakote Sprinkle capsules. The following files are provided for your review:

Depakote ER tablets (NDA 21-168 and NDA 22-267)

- Annotated, redlined label copy in PLR format, MSWORD document
- Redlined label copy in PLR format, MSWORD document
- Clean label copy in PLR format, MSWORD document
- Clean label copy in PLR format, pdf document
- Current Depakote ER package insert, pdf document

Depakote Sprinkle capsules (NDA 19-680)

- Annotated, redlined label copy in PLR format, MSWORD document
- Redlined label copy in PLR format, MSWORD document
- Clean label copy in PLR format, MSWORD document
- Clean label copy in PLR format, pdf document
- Current Depakote Sprinkle capsules package insert, pdf document

Abbott

NDA 21-168; NDA 19-680

Depakote® ER tablets and Depakote Sprinkle capsules

October 31, 2007

Page 2

While the PLR documents have internal hyperlinking, Abbott wishes to point out that the Table of Contents within each document has not been hyperlinked at this time. This will be resolved when the final SPL style sheet rendition is made of the PLR documents.

Waiver Request:

Abbott is requesting a waiver from the Highlights' one-half page requirement under 21 CFR 201.58 for Depakote ER tablets and Depakote Sprinkle capsules. As suggested in the FDA Guidance, Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements, 2006, section V, D., the Highlights section for some drugs with many indications or serious warnings may not condense into one-half page. Depakote ER tablets and Depakote Sprinkle capsules are such products, having a need to present longer sections for Indications and Usage, Dosage and Administration, Warnings and Precautions and Adverse Reactions. The Abbott Medical staff are satisfied that the Highlights' section provides the most important information needed by a practitioner to safely and effectively prescribe the Depakote ER tablets and Depakote Sprinkle capsules products.

This submission is being provided electronically to NDA 21-168, 19-680 and 22-267. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format -General Considerations, IT2 (January 1999), and Providing Regulatory Submissions to in Electronic Format - NDAs, IT3 (January 1999). The submission is comprised of less than 10 megabytes of space. The content was checked for viruses using McAfee VirusScan Enterprise 8.0i and determined to be virus free.

Abbott appreciates your consideration in this matter. Please contact me if you have questions or require additional information.

Sincerely,

ABBOTT LABORATORIES



Steven F. Hoff, R.Ph., Ph.D.
Associate Director
Global Pharmaceutical Regulatory Affairs
Phone: 847-935-6244
Fax: 847-887-8251

NDA 21-168; NDA 19-680
Depakote® ER tablets and Depakote Sprinkle capsules
October 31, 2007
Page 3

Cc:
Tom Laughren, M.D., Director
Division of Psychiatry Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Bates, Doris J

From: Bates, Doris J
Sent: Monday, October 29, 2007 4:31 PM
To: 'Steven F Hoff'
Cc: Bates, Doris J; Ritter, Mark
Subject: NDA 22-267: Depakote Pediatric Submission for Bipolar Disorder: Questions from Psychiatric Clinical Reviewer

Importance: High

Good afternoon Dr. Hoff:

Please refer to your pediatric submissions for Depakote, submitted and received September 24, 2007, and specifically to the submission related to bipolar disorder, which has been assigned Type 6 NDA number 22-267.

Our psychiatric clinical reviewer has the following questions, related to this indication [bipolar disorder] only.

1. Please provide a copy (e-version if it's easier) of the WASH-U-KSADS as a review aid for the clinical reviewer. In particular, the reviewer is interested in the 'expanded mania' supplement section and how the WASH-U-KSADS defines a 'manic' episode.
2. Please explain how you have defined a 'Manic' episode (i.e. please indicate whether you used the "narrow" NIMH phenotype, where patients must have elation, grandiosity AND discrete episodes lasting at least 1 week, or the "broad" phenotype of severe irritability and rapid mood swings).

Please feel free to reply to this email message directly. If you choose to respond by e-mail, please 'reply to all', as this will automatically include our clinical reviewer as a recipient. You should amend the official submission [NDA 22-267, specifically] with copies of any correspondence provided to us in response to these questions, but we can work from e-copies in the interim, and they are generally very helpful.

If you have any questions about this message, please contact me directly, via email or by phone at 301-796-1040.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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

/s/

Doris Bates

10/29/2007 03:34:37 PM

CSO

archived on date sent. see email for time of
transmission to applicant.

Abbott Laboratories
Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60061-6187

**SUBMISSION OF PEDIATRIC STUDY REPORTS
PEDIATRIC EXCLUSIVITY DETERMINATION
REQUESTED**

September 24, 2007

Tom Laughren, M. D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Amendale Road
Beltsville, MD 20705-1266

**Re: Depakote ER (divalproex sodium) extended release tablets
NDA 22-267**

Subject: Prior Approval Supplement: Pediatric Exclusivity and Labeling

Dear Dr. Laughren:

The sponsor, Abbott Laboratories, submits the following information in support of this Prior Approval supplement under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505 and 21 CFR 314.70 (b)(3) for Depakote ER tablets, NDA 22-267. This is a new Type 6 NDA for the purpose of submitting this pediatric labeling supplement. This submission supports safety labeling changes to incorporate pediatric use information for the indication of bipolar disorder-mania. Additionally, the final study reports included within the submission support the claim for Pediatric Exclusivity for Depakote as described by the Federal Food, Drug and Cosmetic Act, section 505A (see item 13, "Claimed Exclusivity").

Full documentation in support of this submission is cross-referenced to the sNDA to Depakote ER tablets, NDA 21-168, submitted on September 24, 2007 to the Division of Neurology Products.

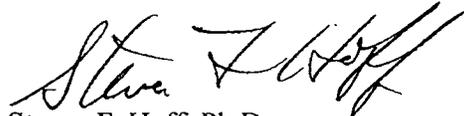
Also, please refer to the August 9, 2002 formal Written Request and the reissued January 31, 2006 formal Written Request (WR).

Abbott

Please contact me at the numbers below if you have any questions or require additional information.

Sincerely,

ABBOTT LABORATORIES

A handwritten signature in black ink, appearing to read "Steve F. Hoff". The signature is fluid and cursive, with the first name "Steve" written in a larger, more prominent script than the last name "Hoff".

Steven F. Hoff, Ph.D.

Associate Director

Global Pharmaceutical Regulatory Affairs

Phone: 847-935-6244

FAX: 847-887-8251

Cc: Cover Letter

Gary Buehler, Director
Office of Generic Drugs
CDER
Food and Drug Administration
FAX: 301-594-0183

SUBMISSION OF PEDIATRIC STUDY REPORTS PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

September 24, 2007

Russell Katz, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Amendale Road
Beltsville, MD 20705-1266

**Re: Depakote ER (divalproex sodium) Extended Release Tablets
NDA 21-168**

Subject: Prior Approval Supplement: Pediatric Exclusivity and Labeling

Dear Dr. Katz:

The sponsor, Abbott Laboratories, submits the following information in support of this Prior Approval supplement under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505 and 21 CFR 314.70 (b)(3) for Depakote ER extended release tablets, NDA 21-168. This submission supports safety labeling changes to incorporate pediatric use information. Additionally, the final study reports included within the submission support the claim for Pediatric Exclusivity for Depakote as described by the Federal Food, Drug and Cosmetic Act, section 505A (see item 13, "Claimed Exclusivity"). The clinical study reports listed below were conducted in compliance with the August 9, 2002 formal Written Request and the reissued January 31, 2006 formal Written Request (WR). All of the studies were listed on www.clinicaltrials.gov. The submitted study reports are as follows:

M01-342: A Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Depakote ER for the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents

M02-555: An Open-Label Long-Term Study to Evaluate the Safety of Depakote Extended Release Tablets in the Treatment of Mania Associated with Bipolar Disorder in Children and Adolescents

M03-647: An Open-Label Study to Evaluate the Safety of Depakote® ER in the Treatment of Mania Associated with Bipolar I Disorder in Children and Adolescents

M02-488: The Safety and Efficacy of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents

M02-554: The Safety of Divalproex Sodium Extended Release Tablets in Migraine Prophylaxis: An Open-Label Extension Study in Adolescents

M03-648: Divalproex Sodium Extended-Release Tablets for Migraine Prophylaxis in Adolescents: An Open-Label, Long-Term Safety Study

M04-714: An Open-Label Multicenter Study of the Long-Term Safety of Depakote® Sprinkle Capsules in the Treatment of Partial Seizures in Children

In addition, the following are provided in this sNDA per the Written Request:

- Pharmacokinetic literature review with calculated age-appropriate dosing regimens for pediatric subjects aged 3-10 years old as described in the Written Request.
- A report on the spontaneous US reporting rate of liver failure resulting in death or transplant associated with valproic acid (VPA) use for epilepsy patients 3-10 years of age and 11-17 years of age during a prescribed period of time. These rates are also provided after stratifying by VPA monotherapy and VPA use in combination with other antiepileptic medications.

For your reviewing convenience please refer to the **annotated Written Request** (see Item 20, "Annotated Written Request"). This submission is a hybrid sNDA using NDA format with CTD formatted documents.

Cross-reference is made to the following NDAs:

18-081 Depakene capsules (epilepsy)

18-082 Depakene syrup (epilepsy)

18-723 Depakote Delayed Release tablets (epilepsy, migraine, mania)

19-680 Depakote Sprinkle capsules (epilepsy)

20-320 Depakote Delayed Release tablets (mania)

20-593 Depacon Injection (epilepsy)

Abbott submitted a proposal for structure and content of this pediatric use supplement on February 27, 2007, and the FDA notified Abbott of their acceptance of the proposal on May 16, 2007, in emails from Ms. Melina Griffis, Senior Regulatory Project Manager. The proposal and FDA acceptance documents are provided in Item 20, Other. The structure and content of this submission are consistent with the above-mentioned proposal.

Contents of the application include:

Item 1. Table of Contents

Item 1 contains the submission cover letter, FDA Form 356h, Establishment Information, Table of Contents and Notes to Reviewer.

Item 2. Labeling

The Package Insert for Depakote ER extended release tablets has been provided in electronic SPL format as an XML file, a PDF file, along with an MSWORD file of a redlined version as a review aid for editing purposes. The currently used and last approved package inserts are also provided as a PDF file. Upon agreement to the final pediatric labeling in this submission, Abbott will provide draft labeling for the labels of other valproate drug products as listed in the above Cross-Referenced NDAs. Final printed labeling for all of the applicable valproate products will be provided upon approval of this supplement.

Pediatric Use information is provided herein based upon the data derived from the aforementioned clinical trials and literature reviews as required by the FDA's Written Request and under 21 CFR 201.57 (f)(9)(iii). The proposed labeling text has been incorporated in the following sections of the Package Insert, **PRECAUTIONS**-Pediatric Use and **ADVERSE REACTIONS**- Mania, Migraine and Epilepsy sections. No efficacy indications or dosing recommendations have been made in the proposed labeling, since the migraine and mania efficacy studies did not reach their primary endpoints.

Item 3. Summary

CTD document 2.5 Clinical Overview is provided in this Item of the sNDA. The Overview provides a full description of the clinical program as it directly relates to the sections of the Written Request.

Item 4. CMC

Not applicable

Item 5. Nonclinical Pharmacology and Toxicology

Not applicable

Item 6. Human Pharmacokinetics

The required pharmacokinetic literature review is provided as CTD document 5.3.3, Human PK Studies. This literature review provides the requested information on pediatric PK parameters as well as suggested dosing regimens derived from this information. Copies of all of the references cited in the PK literature review are provided in Item 6, CTD section 5.4, Literature References.

Item 7. Clinical Microbiology

Not applicable

Item 8. Clinical

Item 8 contains:

- The Summary of Clinical Safety, copies of the references cited therein, synopses of the individual studies, and a tabular listing of the pediatric studies. The Summary of Clinical Safety contains data only from the long-term safety studies.
- NOTE: Safety information from the short term Safety and Efficacy studies are available in the clinical study reports, M01-342 for Bipolar Disorder (Mania) and M02-488 for Migraine prophylaxis. Abbott submitted a proposal for this pediatric use supplement on February 27, 2007, and the FDA notified Abbott of their acceptance of the proposal on May 16, 2007, in emails from Ms. Melina Griffis, Senior Regulatory Project Manager. The structure and content of this submission are consistent with the above-mentioned proposal.
- Final clinical study reports for the above listed pediatric studies.
- A Summary of Clinical Efficacy and a Risk-Benefit Summary are not provided, since efficacy was not demonstrated in the mania or migraine prophylaxis studies.
- Under CTD section 5.3.6 Reports of Postmarketing Experience, a report on the spontaneous US reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy.
- Literature references, compliance with IRB and informed consent regulations, transfer of obligations and the auditing of subject records are also included.

Item 9. Safety Update Report

Not applicable. Please note that Abbott is requesting a waiver in accordance with 21 CFR 314.90, for the four month periodic update of new safety information, "safety update reports", as required under 21 CFR 314.50(d)(5)(vi)(b), in this supplement because no additional studies are currently ongoing or planned for Depakote ER, Depakote DR or Depakote Sprinkle Capsules for the treatment of pediatric indications. Any new information learned about these drugs that may reasonably affect the statement of contraindications, warnings, precautions or adverse events in the draft labeling, will be provided, as appropriate, following discussion with the Agency.

Item 10. Statistical

Not applicable (For electronic submission, items 8 and 10 are identical).

Item 11. Case Report Tabulations

Case Report Tabulations are provided

Item 12. Case Report Forms and Expedited Reports

The Case Report Forms and Expedited Reports are provided for deaths, drop-outs due to adverse events and serious adverse events.

Item 13. Patent Information

FDA Form 3452a and other patent information are provided.

Item 14. Patent Certification

Patent certification is provided

Item 15. Establishment Description

Not applicable

Item 16. Debarment Certification

The Debarment Certification is provided

Item 17. Field Copy Certification

Not applicable

Item 18. User Fee Cover Sheet

FDA Form 3397 along with a copy of the User Fee cover letter and a copy of the User Fee check are provided

Item 19. Financial Information

FDA Forms 3454 and 3455 with financial certification and disclosures are provided.

Item 20. Other

The following are included in Item 20:

- Original Pediatric Written Request, August 9, 2002
- Reissued Pediatric Written Request, January 31, 2006
- **Annotated Written Request**
- Notice of Claim for Exclusivity – Six-Month Pediatric Exclusivity

Written Communications with FDA:

- SPA cover letter for study M01-342, submitted to IND 30,673 (serial 189) on November 6, 2002.

- Dosing rationale included in November 6, 2002 submission
- FDA response to SPA submission sent to Abbott on December 11, 2002.
- New Protocol cover letter for study M01-342, submitted to IND 30,673, serial 191 on March 25, 2003.
- Abbott minutes for September 2, 2004 meeting with FDA regarding amendments to the Pediatric Written Request.

Email Communications with FDA:

- Abbott proposal for structure and format of pediatric submission dated 2-26-07.
- FDA response to proposed structure and format of pediatric submission dated 5-16-07.

- Environmental Assessment – Categorical Exclusion

This submission is being provided electronically. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations, IT2 (January 1999), and Providing Regulatory Submissions in Electronic Format-NDAs, IT3 (January 1999). The submission is comprised of less than 2 Gigabytes of space. The content was checked for viruses using McAfee VirusScan Enterprise 8.0i and was determined to be virus free.

Please contact me at the numbers below if you have any questions or require additional information.

Sincerely,

ABBOTT LABORATORIES



Steven F. Hoff, Ph.D.
Associate Director
Global Pharmaceutical Regulatory Affairs
Phone: 847-935-6244
FAX: 847-887-8251

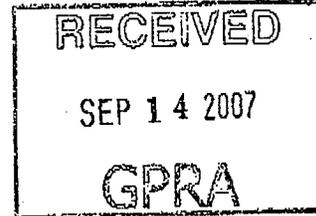
Cc: Cover Letter

Gary Buehler, Director
Office of Generic Drugs
CDER
Food and Drug Administration
FAX: 301-594-0183

to 120

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857NDA 18-081, NDA 18-082, NDA 18-723
NDA 19-680, NDA 20-593, NDA 21-168Abbott
Attention: Steven Hoff, R.Ph., Ph.D.
200 Abbott Park Road, PA76, AP-30-1E
Abbott Park, IL 60064-6157

Dear Dr. Hoff:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for valproate (VPA) delivered in various formulations either as divalproex or valproic acid.

After reviewing both the relevant literature and post-marketing cases of hypothermia with valproic acid, we request that you make the following changes to the **PRECAUTIONS** and **Drug interactions** sections of the prescribing information:

1. We request that you add the following new Precautions subsection:

PRECAUTIONS**Hypothermia**

Hypothermia, defined as an unintentional drop in body core temperature to $<35^{\circ}\text{C}$ (95°F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate (see Drug Interactions, Topiramate). Consideration should be given to stopping valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

2. Please revise the existing Precautions, Hyperammonemia subsection to read as follows:

PRECAUTIONS**Hyperammonemia**

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia (see Precautions; Hypothermia). If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo

investigation for underlying urea cycle disorders (see **CONTRAINDICATIONS** and **WARNINGS - Urea Cycle Disorders (UCD)** and **PRECAUTIONS - Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use**). Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

3. Please revise the existing Precautions, Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use subsection to read as follows:

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see **PRECAUTIONS - Hypothermia**). In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. (see **CONTRAINDICATIONS** and **WARNINGS - Urea Cycle Disorders** and **PRECAUTIONS - Hyperammonemia**).

4. Please revise the Precautions, Drug Interactions, Topiramate subsection to read as follows:

Drug interactions

Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see **CONTRAINDICATIONS** and **WARNINGS - Urea Cycle Disorders** and **PRECAUTIONS - Hyperammonemia and - Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use**). Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported (see **Precautions; Hypothermia and Precautions; Hyperammonemia**).

If you have any questions, call Melina Griffis, R. Ph, Senior Regulatory Project Manager, at (301) 796-1078.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD

Director

Division of Neurology Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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

/s/

Russell Katz
8/31/2007 01:41:26 PM



WRITTEN REQUEST

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168
IND 32,231

Abbott Laboratories
Attention: Steven F. Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491/AP30-1NE
Abbott Park, IL 60064-6157

Dear Dr. Hoff:

Reference is made to your June 22, 2001, Proposed Pediatric Study Request submitted to NDA 21-168 for Depakote ER (divalproex sodium extended-release) Tablets.

To obtain needed pediatric information on valproate (VPA) delivered in various formulations, either as divalproex or valproic acid, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies in migraine prophylaxis, epilepsy and bipolar disorder. We note that the Agency had previously issued a formal Written Request for these products on August 9, 2002; that request, however, expired on August 9, 2005. The Written Request that follows reflects changes to our original request.

PHARMACOKINETICS

Adequate pharmacokinetic information in pediatric patients may be available in the literature. Literature data can be utilized to calculate age-appropriate dosing regimens for pediatric subjects aged 3-10 years described in this Written Request.

Literature references and/or any unpublished data relevant to the calculation of age-appropriate dosing regimens in subjects ages 3 – 10 years and drug-drug interactions must be provided.

Literature review endpoints:

Valproate pharmacokinetic parameters, such as total steady state C_{max}, t_{max}, t_{1/2}, apparent volume of distribution (V/F), C_{min}, free fraction, and total and free apparent clearance (CL/F) must be provided.

Potential effects of covariates such as age and body-weight (or body-surface area) must be included in the analysis to the extent available from the literature, and used in the dosing recommendations if

deemed appropriate. The potential influence of other covariates, such as concomitant medications, on total apparent clearance (CL/F) must also be investigated to the extent available from the literature.

In particular, the effect of other concomitant antiepileptic drugs on the pharmacokinetics of valproate (and vice versa) must be examined in pediatric patients to the extent available from the literature.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of valproate. These results will be compared to pharmacokinetic parameters obtained in adults administered divalproex and/or valproic acid (the use of adult historical control data is acceptable).

MIGRAINE PROPHYLAXIS

Type of Study:

Adolescent Efficacy and Safety Study

Objectives/Rationale:

To evaluate the efficacy and short-term safety of divalproex sodium/valproic acid in the prophylactic treatment of migraine headaches in adolescent patients 12 to 17 years of age.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the prophylactic treatment of migraine headache in adolescent patients, ages 12 to 17 years.

Study Design:

Randomized, double-blind, placebo-controlled, parallel group, dose-response, efficacy and short-term safety outpatient study.

Age Groups to be Studied:

Adolescent patients ages 12 to 17 years, inclusive.

Dose Selections:

Age-appropriate dosing regimens for this study will be based on relevant available data.

Number of Patients to be Studied or Power of the Study to be Achieved:

A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of migraine prevention. The study will be powered using the effect size observed in the pivotal Depakote ER adult study. The study will also attempt to define an interpretable dose-response relationship in this age group, including the identification of a no-effect dose.

Entry Criteria (i.e., inclusion/exclusion criteria):

Adolescent patients between 12 and 17 years of age, with an average of 3-12 IHS (International Headache Society) defined migraine headaches per 28 days. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population. Pregnant patients will be excluded from study enrollment.

Clinical Endpoints:

A single standard measure of migraine attack frequency and measures of clinical safety as defined in the SAFETY section.

Drug Information:

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Statistical Information, Including Statistical Assessments:

Assessment of the between group difference in a standard measure of migraine attack frequency, using an appropriate, prospectively defined statistical methodology, and a descriptive analysis of the safety data.

Labeling That May Result from this Study:

The adolescent migraine efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets, or vice versa.

PARTIAL SEIZURES

Type of Study:

Pediatric Long-term Safety Study

Objectives/Rationale:

To establish the long-term safety of divalproex sodium/valproic acid in the treatment of partial seizures in pediatric patients ages 3 years to 10 years.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the treatment of partial seizures in pediatric patients, ages 3 to 10 years.

Study Design:

Open-label, multicenter, long-term outpatient safety study.

Age Groups to be Studied:

Pediatric patients ages 3 years to 10 years.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on current divalproex sodium/valproic acid labeling for epilepsy and at investigator's discretion.

Number of Patients to be Studied or Power of the Study to be Achieved:

A sufficient number of pediatric patients with partial seizures to provide data on approximately 50 patients, ages 3 years to 10 years, exposed to study drug for one year.

Entry Criteria (i.e., inclusion/exclusion criteria):

Pediatric patients ages 3 years to 10 years with partial seizures. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints:

Measures of clinical safety as defined in SAFETY section, in addition to measure of seizure frequency.

Drug Information:

Dosage form: Age-appropriate oral formulation.

Route of administration: Oral

Regimen: Based on current divalproex sodium/valproic acid epilepsy labeling recommendations and at investigator's discretion.

Statistical Information, Including Statistical Assessments:

Descriptive statistics of safety data must be provided.

Labeling That May Result from this Study:

The pediatric epilepsy safety study described in this request may result in the addition to labeling of information pertinent to this study.

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder:

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach also requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations.

We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group (but see below, "Safety" and "Pharmacokinetics"). For pediatric mania, we consider the relevant age group to include adolescents aged 10-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Type of Study:

Pediatric Efficacy and Safety Study

Objective/Rationale:

The overall goal of the development program would be to establish the safety and efficacy of divalproex sodium/valproic acid in the treatment of adolescent mania in association with bipolar disorder.

Study Design:

For the controlled efficacy study, conduct a randomized, double-blind, parallel group, placebo-controlled acute bipolar disorder trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete the trial (i.e. have a Week 4 efficacy evaluation), in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed-dose study including at least two fixed doses of the study drug. Given the lack of a robust

evidence base for the use of divalproex sodium/valproic acid in adolescent mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium.

The trial will be limited to patients capable of giving assent to participate in the trial.

Age Group in Which Studies will be Performed:

Adolescents (ages 10 to 17 years) must be included in the sample. Enrollment will reflect the gender, age, and racial distribution concordant with this patient population. No pregnant patients will be included.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on relevant available data from the medical literature.

Number of Patients to be Studied:

The study must have a sufficient number of patients to provide reasonable statistical power to demonstrate a clinically and statistically meaningful difference between drug and placebo. It should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It may be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Entry Criteria:

The protocol(s) must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is required that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also required that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Pregnant patients will be excluded from study enrollment.

Patient Evaluations and Study Endpoints:

A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population will be used. A global measure, e.g., the Clinical Global Impression (CGI) may be included. A primary outcome (or outcomes if more than one is considered important) must be prospectively identified for the controlled efficacy trials. This may include "change from baseline to endpoint" on whatever symptom rating scale has been chosen for the trial(s).

Statistical Information:

A detailed statistical plan will be prospectively provided. The trial will be designed with adequate statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults).

Drug Information:

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 10 to 17), your marketed solid dosage formulation may be adequate for these studies.

Labeling that May Result from the Studies:

The pediatric mania efficacy and safety study described in this Written Request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets. Likewise, the current claims for adult patients for Depakote Tablets could be extended to Depakote ER.

SAFETY

Safety data must be collected in all of the trials for the above indications. Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e. vital signs, weight, height, clinical laboratory measures, ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias).

Safety concerns deserving special attention include: hepatotoxicity and hyperammonemia (baseline LFTs and ammonia levels with monthly follow-up testing for 3 months), pancreatitis (baseline amylase levels with monthly follow-up testing for 3 months), thrombocytopenia, rash, cognitive/neuropsychiatric adverse events, and effects on growth.

Cognitive/neuropsychiatric, behavior, and movement assessments must be conducted in an open-label, long-term safety study in migraine prophylaxis, an open-label, long-term safety study in bipolar disorder, and an open-label, long-term safety study in partial seizures. Cognitive/neuropsychiatric assessments using an age-appropriate scale (e.g. Wechsler or Development-Profile II) must be conducted at baseline with periodic testing (e.g. every 6 months). Behavior assessments (e.g. Parent rating scale of the Behavior Assessment System for Children) must be conducted at baseline with periodic testing (e.g. every 6 months). Movement assessments (e.g. movement-related items from the UKU Side Effects Scale) must be conducted at baseline with periodic testing (e.g. every 3 to 6 months).

Because divalproex sodium/valproic acid has recently been developed for partial complex seizures in patients as young as 10 years of age, systematically-collected safety data exists for epilepsy patients 10 to 17 years of age.

For the open-label, long-term safety study in partial seizures, approximately 50 patients, age 3 to 10 years, must be exposed to study drug for one year.

For the study in partial seizures, we have only asked for enrollment of children 3 years of age and older because polytherapy in patients less than 3 years is associated with an elevated risk of hepatic fatality. To meet the terms of this written request, provide the spontaneous U.S. reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy in patients 3-10 years of age and 11-17 years of age received during the period of January 1, 2002 up to a date no earlier than 10 months

NDA 18-723 NDA 19-680 NDA 20-320
NDA 20-593 NDA 20-782 NDA 21-168
IND 32,231
Page 8

prior to your complete response to this letter. Additionally, provide these rates after stratifying by VPA monotherapy and VPA use in combination with other antiepileptic medications.

For the migraine indication, a sufficient number of adolescent migraine patients, between 12 and 17 years of age, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used to prevent migraine attacks over one year must be assessed. Enrollment must be adequate to obtain well-characterized safety data at clinically relevant doses from approximately 150 subjects in the relevant populations treated for 6 months and approximately 75 subjects treated for one year.

For the adolescent bipolar disorder indication, a sufficient number of adolescent patients, ages 10 to 17 years, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used as monotherapy or adjunctive therapy (with divalproex sodium/valproic acid) to treat adolescent mania in association with bipolar disorder must be enrolled to ensure that approximately 100 patients will be exposed to study drug for at least six months.

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before October 7, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

NDA 18-723 NDA 19-680 NDA 20-320
NDA 20-593 NDA 20-782 NDA 21-168
IND 32,231
Page 10

If you have any questions, call Courtney Calder, Pharm.D., Regulatory Project Manager, at 301-796-1050

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I

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

/s/

Robert Temple
1/31/2006 07:08:45 PM



WRITTEN REQUEST – AMENDMENT 2

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168
IND 32,231

Abbott Laboratories
Attention: Steven F. Hoff, Ph.D.
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491/AP30-1NE
Abbott Park, IL 60064-6157

Dear Mr. Muroka:

Please refer to your correspondence dated October 27, 2004, requesting changes to FDA's August 9, 2002 Written Request for pediatric studies for valproate (VPA).

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated August 9, 2002.

PHARMACOKINETICS

Adequate pharmacokinetic information in pediatric patients may be available in the literature. Literature data can be utilized to calculate age-appropriate dosing regimens for pediatric subjects aged 3-10 years described in this Written Request.

Literature references and/or any unpublished data relevant to the calculation of age-appropriate dosing regimens in subjects ages 3 – 10 years and drug-drug interactions must be provided.

Literature review endpoints:

Valproate pharmacokinetic parameters, such as total steady state C_{max}, t_{max}, t_{1/2}, apparent volume of distribution (V/F), C_{min}, free fraction, and total and free apparent clearance (CL/F) must be provided.

Potential effects of covariates such as age and body-weight (or body-surface area) must be included in the analysis to the extent available from the literature, and used in the dosing recommendations if deemed appropriate. The potential influence of other covariates, such as concomitant medications, on total apparent clearance (CL/F) must also be investigated to the extent available from the literature.

NDA 18-723; NDA 19-680; NDA 20-320
NDA 20-593; NDA 20-782; NDA 21-168
IND 32,231
Page 2

In particular, the effect of other concomitant antiepileptic drugs on the pharmacokinetics of valproate (and vice versa) must be examined in pediatric patients to the extent available from the literature.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of valproate. These results will be compared to pharmacokinetic parameters obtained in adults administered divalproex and/or valproic acid (the use of adult historical control data is acceptable).

MIGRAINE PROPHYLAXIS

Type of Study:

Adolescent Efficacy and Safety Study

Objectives/Rationale:

To evaluate the efficacy and short-term safety of divalproex sodium/valproic acid in the prophylactic treatment of migraine headaches in adolescent patients 12 to 17 years of age.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the prophylactic treatment of migraine headache in adolescent patients, ages 12 to 17 years.

Study Design:

Randomized, double-blind, placebo-controlled, parallel group, dose-response, efficacy and short-term safety outpatient study.

Age Groups to be Studied:

Adolescent patients ages 12 to 17 years, inclusive.

Dose Selections:

Age-appropriate dosing regimens for this study will be based on relevant available data.

Number of Patients to be Studied or Power of the Study to be Achieved:

A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of migraine prevention. The study will be powered using the effect size observed in the pivotal Depakote ER adult study. The study will also attempt to define an interpretable dose-response relationship in this age group, including the identification of a no-effect dose.

Entry Criteria (i.e., inclusion/exclusion criteria):

Adolescent patients between 12 and 17 years of age, with an average of 3-12 IHS (International Headache Society) defined migraine headaches per 28 days. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population. Pregnant patients will be excluded from study enrollment.

Clinical Endpoints:

A single standard measure of migraine attack frequency and measures of clinical safety as defined in the SAFETY section.

Drug Information:

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Statistical Information, Including Statistical Assessments:

Assessment of the between group difference in a standard measure of migraine attack frequency, using an appropriate, prospectively defined statistical methodology, and a descriptive analysis of the safety data.

Labeling That May Result from this Study:

The adolescent migraine efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets, or vice versa.

PARTIAL SEIZURES

Type of Study:

Pediatric Long-term Safety Study

Objectives/Rationale:

To establish the long-term safety of divalproex sodium/valproic acid in the treatment of partial seizures in pediatric patients ages 3 years to 10 years.

Indication to be Studied:

The use of divalproex sodium/valproic acid for the treatment of partial seizures in pediatric patients, ages 3 to 10 years.

NDA 18-723; NDA 19-680; NDA 20-320
NDA 20-593; NDA 20-782; NDA 21-168
IND 32,231
Page 4

Study Design:

Open-label, multicenter, long-term outpatient safety study.

Age Groups to be Studied:

Pediatric patients ages 3 years to 10 years.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on current divalproex sodium/valproic acid labeling for epilepsy and at investigator's discretion.

Number of Patients to be Studied or Power of the Study to be Achieved:

A sufficient number of pediatric patients with partial seizures to provide data on approximately 50 patients, ages 3 years to 10 years, exposed to study drug for one year.

Entry Criteria (i.e., inclusion/exclusion criteria):

Pediatric patients ages 3 years to 10 years with partial seizures. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints:

Measures of clinical safety as defined in SAFETY section, in addition to measure of seizure frequency.

Drug Information:

Dosage form: Age-appropriate oral formulation.

Route of administration: Oral

Regimen: Based on current divalproex sodium/valproic acid epilepsy labeling recommendations and at investigator's discretion.

Statistical Information, Including Statistical Assessments:

Descriptive statistics of safety data must be provided.

Labeling That May Result from this Study:

The pediatric epilepsy safety study described in this request may result in the addition to labeling of information pertinent to this study.

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder:

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach also requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations.

We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group (but see below, "Safety" and "Pharmacokinetics"). For pediatric mania, we consider the relevant age group to include adolescents aged 10-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Type of Study:

Pediatric Efficacy and Safety Study

Objective/Rationale:

The overall goal of the development program would be to establish the safety and efficacy of divalproex sodium/valproic acid in the treatment of adolescent mania in association with bipolar disorder.

Study Design:

For the controlled efficacy study, conduct a randomized, double-blind, parallel group, placebo-controlled acute bipolar disorder trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete the trial (i.e. have a Week 4 efficacy evaluation), in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed-dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of divalproex sodium/valproic acid in adolescent mania, there is uncertainty

about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium.

The trial will be limited to patients capable of giving assent to participate in the trial.

Age Group in Which Studies will be Performed:

Adolescents (ages 10 to 17 years) must be included in the sample. Enrollment will reflect the gender, age, and racial distribution concordant with this patient population. No pregnant patients will be included.

Dose Selection:

An age-appropriate dosing regimen for this study will be based on relevant available data from the medical literature.

Number of Patients to be Studied:

The study must have a sufficient number of patients to provide reasonable statistical power to demonstrate a clinically and statistically meaningful difference between drug and placebo. It should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It may be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Entry Criteria:

The protocol(s) must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is required that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also required that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Pregnant patients will be excluded from study enrollment.

Patient Evaluations and Study Endpoints:

A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population will be used. A global measure, e.g., the Clinical Global Impression (CGI) may be included. A primary outcome (or outcomes if more than one is considered important) must be prospectively identified for the controlled efficacy trials. This may include "change from baseline to endpoint" on whatever symptom rating scale has been chosen for the trial(s).

Statistical Information:

A detailed statistical plan will be prospectively provided. The trial will be designed with adequate statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults).

Drug Information:

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 10 to 17), your marketed solid dosage formulation may be adequate for these studies.

Labeling that May Result from the Studies:

The pediatric mania efficacy and safety study described in this Written Request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets. Likewise, the current claims for adult patients for Depakote Tablets could be extended to Depakote ER.

SAFETY

Safety data must be collected in all of the trials for the above indications. Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e. vital signs, weight, height, clinical laboratory measures, ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias).

Safety concerns deserving special attention include: hepatotoxicity and hyperammonemia (baseline LFTs and ammonia levels with monthly follow-up testing for 3 months), pancreatitis (baseline amylase levels with monthly follow-up testing for 3 months), thrombocytopenia, rash, cognitive/neuropsychiatric adverse events, and effects on growth.

Cognitive/neuropsychiatric, behavior, and movement assessments must be conducted in an open-label, long-term safety study in migraine prophylaxis, an open-label, long-term safety study in bipolar disorder, and an open-label, long-term safety study in partial seizures. Cognitive/neuropsychiatric assessments using an age-appropriate scale (e.g. Wechsler or Development-Profile II) must be conducted at baseline with periodic testing (e.g. every 6 months). Behavior assessments (e.g. Parent rating scale of the Behavior Assessment System for Children) must be conducted at baseline with periodic testing (e.g. every 6 months). Movement assessments (e.g. movement-related items from the UKU Side Effects Scale) must be conducted at baseline with periodic testing (e.g. every 3 to 6 months).

Because divalproex sodium/valproic acid has recently been developed for partial complex seizures in patients as young as 10 years of age, systematically-collected safety data exists for epilepsy patients 10 to 17 years of age.

For the open-label, long-term safety study in partial seizures, approximately 50 patients, age 3 to 10 years, must be exposed to study drug for one year.

For the study in partial seizures, we have only asked for enrollment of children 3 years of age and older because polytherapy in patients less than 3 years is associated with an elevated risk of hepatic fatality. To meet the terms of this written request, provide the spontaneous U.S. reporting rate of liver failure resulting in death or transplant associated with VPA use for epilepsy in patients 3-10 years of age and 11-17 years of age received during the period of January 1, 2002 up to a date no earlier than 10 months

NDA 18-723; NDA 19-680; NDA 20-320
NDA 20-593; NDA 20-782; NDA 21-168
IND 32,231
Page 8

prior to your complete response to this letter. Additionally, provide these rates after stratifying by VPA monotherapy and VPA use in combination with other antiepileptic medications.

For the migraine indication, a sufficient number of adolescent migraine patients, between 12 and 17 years of age, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used to prevent migraine attacks over one year must be assessed. Enrollment must be adequate to obtain well-characterized safety data at clinically relevant doses from approximately 150 subjects in the relevant populations treated for 6 months and approximately 75 subjects treated for one year.

For the adolescent bipolar disorder indication, a sufficient number of adolescent patients, ages 10 to 17 years, to be able to characterize the long-term safety of divalproex sodium/valproic acid when used as monotherapy or adjunctive therapy (with divalproex sodium/valproic acid) to treat adolescent mania in association with bipolar disorder must be enrolled to ensure that approximately 100 patients will be exposed to study drug for at least six months.

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before October 7, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

If you have any questions, call Courtney Calder, Pharm.D., Regulatory Project Manager, at 301-796-1050.

NDA 18-723; NDA 19-680; NDA 20-320
NDA 20-593; NDA 20-782; NDA 21-168
IND 32,231
Page 10

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I

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this page is the manifestation of the electronic signature.**

/s/

Robert Temple
12/21/2005 02:58:47 PM



NDA 21-168 / S-012

Abbott Laboratories
Attention: Lee M. Muraoka, BSPHarm, 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.

In addition, we note that supplemental application S-009 to this same NDA, submitted November 17, 2003 and received November 18, 2003, is currently pending in the Division of Neurology Products. It is our understanding that this application, when approved, will provide for specific amendments to the labeling for Depakote ER that will increase the safe use of this product, independent of the indication for which it is administered.

Therefore, if NDA 21-168 / S-009 is approved within 30 days of the date of this letter, we request that you submit final printed labeling (FPL), reflecting the combined labeling changes under S-009 and S-012, to both supplemental applications.

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.h17.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), with additional revisions as noted above, pending approval of S-009 to this NDA.

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: as noted, this may require further revision in accordance with approval of S-009]

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/s/

Thomas Laughren
12/6/2005 08:01:36 AM



Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 21-168

Abbott Laboratories
Attn: Lee Muraoka
Department 491, Building AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Mr. Townsend:

Please refer to the Written Request, originally issued on August 9, 2002 that you received from the Center for Drug Evaluation and Research.

BPCA § 18: Minority Children and Pediatric Exclusivity Program

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

Format of reports to be submitted:

In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request issued or re-issued under BPCA and filed by FDA, regardless of the following circumstances:

- (1) the type of response to the Written Request (complete or partial);
- (2) the status of the supplement (withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e. approval, approvable, not approvable); or
- (4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at [<http://www.fda.gov/cder/pediatric/Summaryreview.htm>] and publish in the Federal Register a notification of availability.

Page 2

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug
Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy

5/7/04 04:24:16 PM



Abbott Laboratories
Attention: Mr. Steven E. Townsend
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

Dear Mr. Townsend:

Reference is made to your Proposed Pediatric Study Request (PPSR) submitted on June 22, 2001 for Depakote ER (divalproex sodium extended-release) Tablets NDA 21-168.

To obtain needed pediatric information on valproate (VPA) delivered in various formulations, either as divalproex or valproic acid, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies in migraine prophylaxis, epilepsy and bipolar disorder.

PHARMACOKINETICS

Type of Study

Pharmacokinetic Study in Pediatric Patients (3-17 years of age)

The pharmacokinetic information of valproate after divalproex and/or valproic acid administration in pediatric patients can be generated in one study, and utilized for all indications (migraine prophylaxis, epilepsy, and bipolar disorder).

If different formulations will be used in the clinical trials, the relative bioavailability between the formulations must be established or known (the use of bioavailability data generated in adults is acceptable).

Objectives/Rationale

To characterize the pharmacokinetics of valproate in the pediatric patient population to determine age-appropriate dosing regimens in the pediatric efficacy and safety studies for the different indications described in this Written Request.

We acknowledge that adequate pharmacokinetic information in pediatric patients may be available in the literature. Literature data can be utilized to calculate age-appropriate dosing regimens for the pediatric efficacy and safety studies described in this Written Request. In such a situation, in lieu of a separate pharmacokinetic study in pediatric patients 3-17 years old, submit the following:

1. Literature references and/or any unpublished data relevant to the calculation of age-appropriate dosing regimens and drug-drug interactions.
2. Confirmation of dose selection (from literature and/or unpublished data) and drug-drug interactions by a population pharmacokinetic assessment (sparse sampling approach) in the pediatric

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 2

efficacy/safety study for the treatment of partial seizures. This population assessment must, in fact, be performed even if you conduct a traditional pharmacokinetic study.

3. The pharmacokinetics of valproate must be evaluated after Depakote ER administration in patients aged 8 – 17 years or lower, if the lower age limit specified in the inclusion criteria of the efficacy/safety study is <8 years.

Age groups and number of patients to be studied:

- Pediatric patients 3 - 17 years of age, with approximate uniform distribution of patients throughout the age range. Enrollment will generally reflect the gender, age, and racial distribution concordant with patient populations for all indications (migraine prophylaxis, epilepsy, and bipolar disorder).
- A sufficient number of pediatric patients to adequately characterize the pharmacokinetics of valproate within the age range (3 - 17 years).

Study design:

For all ages of the pediatric patients, the pharmacokinetic study design must be either a traditional design (frequent sampling) or a population design (sparse sampling). If a sparse sampling approach is followed, approximately 3-4 blood samples per patient in 3-4 time brackets will be collected, instead of blood samples at 3-4 fixed time points covering the full concentration-time profile after the divalproex dose.

Study endpoints:

Valproate (total and free as appropriate) pharmacokinetic parameters, such as C_{max} , t_{max} , AUC, $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution (V/F) must be calculated.

Potential effects of covariates such as age and body-weight (or body-surface area) must be included in the analysis, and used in the dosing recommendations if deemed appropriate. The potential influence of other covariates, such as gender or concomitant medications, on the above mentioned pharmacokinetic parameters should also be investigated.

In particular, the effect of other concomitant antiepileptic drugs on the pharmacokinetics of valproate (and vice versa) should be examined in pediatric patients.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of valproate. These results will be compared to pharmacokinetic parameters obtained in adults administered divalproex and/or valproic acid (the use of adult historical control data is acceptable).

Drug information:

Dosage form: Age appropriate divalproex formulation

Route of administration: Oral

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 3

MIGRAINE PROPHYLAXIS

Type of Study

Adolescent Efficacy and Safety Study

Objectives/Rationale

To evaluate the efficacy and short-term safety of VPA in the prophylactic treatment of migraine headaches in adolescent patients 12 to 17 years of age.

Indication to be Studied

The use of VPA for the prophylactic treatment of migraine headache in adolescent patients, ages 12 to 17 years.

Study Design

Randomized, double-blind, placebo-controlled, parallel group, dose-response, efficacy and short-term safety outpatient study.

Age Groups to be Studied

Adolescent patients ages 12 to 17 years, inclusive.

Dose Selections

Age-appropriate dosing regimens for this study will be based on relevant available data from the medical literature and/or on the pharmacokinetics studies described in this Written Request.

Number of Patients to be Studied or Power of the Study to be Achieved

A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of migraine prevention. The study will be powered using the effect size observed in the pivotal adult studies. The study will also define an interpretable dose-response relationship in this age group, including the identification of a no-effect dose.

Entry Criteria (i.e., inclusion/exclusion criteria)

Adolescent patients between 12 and 17 years of age, with an average of 3-12 IHS (International Headache Society) defined migraine headaches per 28 days. Enrollment will reflect the gender, age, and racial distribution concordant with this patient population. Pregnant patients will be excluded from study enrollment.

Clinical Endpoints

A single standard measure of migraine attack frequency and measures of clinical safety as defined in the SAFETY section.

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 4

Drug Information

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Formulation: solid oral dosage form

Statistical Information, Including Statistical Assessments

Assessment of the between group difference in a standard measure of migraine attack frequency, using an appropriate, prospectively defined statistical methodology, and a descriptive analysis of the safety data.

Labeling That May Result from this Study

The adolescent migraine efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets, or vice versa.

PARTIAL SEIZURES

Type of Study

Pediatric Efficacy and Safety Study

Objectives/Rationale

To establish the efficacy and short-term safety of VPA as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 3 years to 10 years.

Indication to be Studied

The use of VPA for the adjunctive treatment of partial seizures in pediatric patients, ages 3 to 10 years

Study Design

Randomized, double-blind, placebo-controlled, parallel group, dose-response, efficacy and short-term safety outpatient study.

Age Groups to be Studied

Pediatric patients ages 3 years to 10 years.

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 5

Dose Selection

An age-appropriate dosing regimen for this study will be based on relevant available data from the medical literature and/or on the pharmacokinetic studies described in this Written Request.

Number of Patients to be Studied or Power of the Study to be Achieved

A sufficient number of pediatric patients with partial seizures to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of seizure prevention. The study will be powered using the effect size observed in the pivotal adult studies. The study will define the dose-response relationship in this age group.

Entry Criteria (i.e., inclusion/exclusion criteria)

Pediatric patients ages 3 years to 10 years with refractory partial seizures, uncontrolled on one or more standard antiepileptic drugs. Enrollment will generally reflect the gender, age, and racial distribution concordant with this patient population.

Clinical Endpoints

A single standard measure of seizure frequency and measures of clinical safety as defined in SAFETY section.

Drug Information

Dosage form: Oral tablet for older pediatric patients or other age-appropriate formulation for younger patients.

Route of administration: Oral

Regimen: To be determined by the development plan

Statistical Information, Including Statistical Assessments

Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and a descriptive analysis of the safety data.

Labeling That May Result from this Study

The pediatric epilepsy efficacy and safety study described in this request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for pediatric patients for Depakote ER could be extended to Depakote Tablets as well as other VPA products. Likewise, the current claims for adult patients for Depakote Tablets could be extended to Depakote ER.

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 6

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 13 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group (but see below, "Safety" and "Pharmacokinetics"). For pediatric mania, we consider the relevant age group to include adolescents aged 13-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Type of Study:

Pediatric Efficacy and Safety Study

Objective/Rationale:

The overall goal of the development program would be to establish the safety and efficacy of VPA in the treatment of adolescent mania in association with bipolar disorder.

Study Design

For the controlled efficacy study, conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete the trial to the nominal endpoint on study drug, in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of VPA in adolescent mania, there is uncertainty about the optimal therapeutic approach in this

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 7

population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking VPA.

You may also consider a relapse prevention trial to follow from the acute treatment trial, in which responders to acute treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients.

Both the acute and the relapse prevention trials will be limited to patients capable of giving assent to participate in the trial.

Age Group in Which Studies will be Performed

Adolescents (ages 13 to 17 years) must be included in the sample. Enrollment will reflect the gender, age, and racial distribution concordant with this patient population. No pregnant patients will be included.

Dose Selection

An age-appropriate dosing regimen for this study will be based on relevant available data from the medical literature and/or on the pharmacokinetics studies described in this Written Request.

Number of Patients to be Studied

The study must have a sufficient number of patients to provide reasonable statistical power to demonstrate a clinically and statistically meaningful difference between drug and placebo. It should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It may be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Entry Criteria

The protocol(s) must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is required that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also required that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Pregnant patients will be excluded from study enrollment.

Patient Evaluations and Study Endpoints

A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population will be used. A global measure, e.g., the Clinical Global Impression (CGI) may be included. A primary outcome (or outcomes if more than one is considered important) must be prospectively identified for the controlled efficacy trials. This may include "change from baseline to endpoint" on whatever symptom rating scale has been chosen for the trial(s).

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 8

Statistical Information

A detailed statistical plan will be prospectively provided. The trial will be designed with adequate statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults).

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 13 to 17), your marketed solid dosage formulation may be adequate for these studies.

Labeling that May Result from the Studies

The pediatric mania efficacy and safety study described in this Written Request may result in the addition to labeling of information pertinent to this study. If Depakote ER is the formulation used in this study, any resulting claims for adolescent patients for Depakote ER could be extended to Depakote Tablets. Likewise, the current claims for adult patients for Depakote Tablets could be extended to Depakote ER.

SAFETY

Safety data must be collected in all of the controlled efficacy trials for the above indications. Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e. vital signs, weight, height, clinical laboratory measures, ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias).

Safety concerns deserving special attention include: hepatotoxicity and hyperammonemia (baseline LFTs and ammonia levels with monthly follow-up testing for 3 months), pancreatitis (baseline amylase levels with monthly follow-up testing for 3 months), thrombocytopenia, rash, cognitive/neuropsychiatric adverse events, and effects on growth.

Valproate products have been marketed in the U.S. and widely used in pediatric patients for over 20 years. We acknowledge that you have already collected a substantial amount of long-term safety data in pediatric epilepsy patients exposed to VPA, both as adjunctive and monotherapy. However, if you intend to rely on long-term safety data in pediatric epilepsy patients to support chronic treatment in migraine and adolescent bipolar disorder, then you will need to make the case that the pediatric epilepsy long-term experience is applicable to the adolescent migraine and bipolar populations. Much of the pediatric epilepsy experience will be as adjunctive therapy and the safety data from such experience may not be directly applicable to use as monotherapy in other clinical settings.

Because VPA has recently been developed for partial complex seizures in patients as young as 10 years of age, systematically-collected safety data exists for patients 10 to 17 years of age and may satisfy the need for long-term adolescent safety data in migraine and bipolar disorder (see below).

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 9

Because VPA was approved for absence seizures so long ago, the safety data may not have been collected systematically, by today's standards; a single adequate safety database may not exist for patients less than 11 years. You may be able to compile safety data from various sources, to include published literature, to partially satisfy the need for long-term safety data in patients less than 10 years old.

For the migraine indication, a sufficient number of adolescent migraine patients, between 12 and 17 years of age, to be able to characterize the long-term safety of VPA when used to prevent migraine attacks over one year will be assessed. Enrollment must be adequate to ensure that a minimum of 300 patients, using the highest planned marketed dose exposed for six months, and a minimum of 100 patients, using the highest planned marketed dose exposed for one year, will complete the study. As stated above, you may wish to argue that other experience (adjunctive therapy in epilepsy) is relevant and can be substituted for part or all of this requirement. If that is your intention, you must submit your argument in writing for the Division's review along with a request for an amendment to this Pediatric Written Request. Your intention regarding such an amendment should be stated in your Response (see RESPONSE TO WRITTEN REQUEST below) so that such an amendment can be reviewed in a timely manner.

For adjunctive efficacy studies in partial seizures, we have only asked for evidence of effectiveness in children 3 years of age and older because polytherapy in patients less than 3 years is associated with an elevated risk of hepatic fatality. To meet the terms of this written request, provide an overall estimate of the rate of liver failure resulting in death or transplant associated with VPA use. Additionally, calculate this rate after stratifying by age and number of concomitant medications.

For the partial seizure indication, a minimum of 100 patients, age 3 to 10 years must be exposed to study drug for one year.

For the adolescent bipolar disorder indication, a sufficient number of adolescent patients, ages 13 to 17 years, to be able to characterize the long-term safety of VPA when used as monotherapy or adjunctive therapy (with VPA) to treat adolescent mania in association with bipolar disorder will be enrolled to ensure that a minimum of 100 patients be exposed to study drug for at least six months. As stated above for the migraine indication, other experience (adjunctive therapy in epilepsy) may be relevant and might be substituted for a part of this requirement with our Division's agreement. If that is your intention, you must submit your argument in writing for the Division's review along with a request for an amendment to this Pediatric Written Request. Your intention regarding such an amendment should be stated in your Response (see RESPONSE TO WRITTEN REQUEST below) so that such an amendment can be reviewed in a timely manner.

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 10

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a **new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

NDA 18-723
NDA 19-680
NDA 20-320
NDA 20-593
NDA 20-782
NDA 21-168

Page 11

If you have any questions, call Lana Chen, Regulatory Project Manager, at 301-594-5529.

Sincerely,

{See appended electronic signature page}

Rachel E. Behrman, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Rachel Behrman
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