

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-446**

**Administrative/Correspondence Reviews**

### 13. PATENT AND MARKET EXCLUSIVITY INFORMATION

#### 13.1 Patent Information

Pursuant to 21 C.F.R. § 314.53, an FDA Form 3542a has been included with this NDA for each of the following U.S. patents:

- A. United States Patent Number: 6,197,819 B1  
Expiration Date: March 6, 2018  
Patent Type: Compound per se and pharmaceutical composition
- B. United States Patent Number: 5,563,175  
Expiration Date: October 8, 2013  
Patent Type: Method of use for seizure disorders
- C. US Patent Number: 6,001,876  
Expiration Date: July 16, 2017  
Patent Type: Method of use for treating pain
- D. US Patent Number: 6,117,906  
Expiration Date: October 8, 2013  
Patent Type: Method of use for treating anxiety

#### 13.2 Claim of Marketing Exclusivity

The following information is submitted pursuant to 21 C.F.R. § 314.50(j):

- (1) Parke-Davis, a Division of Pfizer, Inc, hereby claims five (5) years of marketing exclusivity for LYRICA<sup>TM</sup> (pregabalin) 25, 50, 75, 100, 150, 200 and 300 mg capsules.
- (2) This claim is supported by 21 C.F.R. § 314.108(b)(2), as well as 21 U.S.C. §§ 355(j)(5)(D)(ii) and 355(c)(3)(D)(ii).
- (3) Parke-Davis, a Division of Pfizer, Inc, hereby certifies that, to the best of its knowledge or belief, the active moiety pregabalin has not previously been approved in an application submitted under 21 U.S.C. § 355(b).

**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

21-446

NAME OF APPLICANT / NDA HOLDER

Parke-Davis, Division of Pfizer Inc

*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)

Lynica

ACTIVE INGREDIENT(S)

Pregabalin  
s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid

STRENGTH(S)

25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg

DOSAGE FORM

Oral Capsules

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

6,197,819

b. Issue Date of Patent

3/6/2001

c. Expiration Date of Patent

3/6/2018

d. Name of Patent Owner

Northwestern University  
Attn: Dr. Indrani Mukharji  
Director, Technology Transfer Department

Address (of Patent Owner)

1880 Oak Avenue, Suite 100

City/State

Evanston, Illinois

ZIP Code

60201-3135

FAX Number (if available)

847-491-3625

Telephone Number

847-491-2105

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)

N/A

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) 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

*Karen DeBenedictis*

10/8/03

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

Karen DeBenedictis

Address

Pfizer Inc  
2800 Plymouth Rd.

City/State

Ann Arbor, Michigan

ZIP Code

48105

Telephone Number

734-622-3374

FAX Number (if available)

734-622-2928

E-Mail Address (if available)

Karen.DeBenedictis@pfizer.com

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.*

**PATENT INFORMATION SUBMITTED WITH THE  
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Composition) and/or Method of Use*

NDA NUMBER

21-446.

NAME OF APPLICANT / NDA HOLDER

Parke-Davis, Division of Pfizer Inc

*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)

Lyrica

ACTIVE INGREDIENT(S)

Pregabalin  
s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid

STRENGTH(S)

25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg

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**1. GENERAL**

a. United States Patent Number  
5,563,175

b. Issue Date of Patent  
10/8/1996

c. Expiration Date of Patent  
10/8/2013

d. Name of Patent Owner  
Warner-Lambert Company LLC (see address, phone, fax to right)  
Attn: Charles Ashbrook, Esq.  
2800 Plymouth Road  
Ann Arbor, Michigan 48105  
734-622-5215  
fax=734-622-1553

Address (of Patent Owner)  
201 Tabor Road

City/State  
Morris Plains, New Jersey

ZIP Code  
07950

FAX Number (if available)  
734-622-1553

2<sup>nd</sup> Patent Owner  
Northwestern University  
Attn: Dr. Indrani Mukharji  
Director, Technology Transfer department  
1880 Oak Avenue, Suite 100  
Evanston, Illinois 60201-3135  
847-491-2105  
fax=847-491-3625

Telephone Number  
734-622-5215

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 f.e.)  
N/A

City/State

ZIP Code

FAX Number (if available)

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) 1 (one) 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.)

[ ]

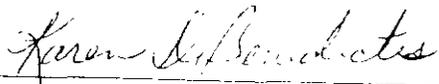
**5. No Relevant Patents**

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

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 10/8/03

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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  
Karen DeBenedictis

Address  
Pfizer Inc  
2800 Plymouth Road

City/State  
Ann Arbor, Michigan

ZIP Code  
48105

Telephone Number  
734-622-3374

FAX Number (if available)  
734-622-2928

E-Mail Address (if available)  
Karen.DeBenedictis@pfizer.com

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

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**PATENT INFORMATION SUBMITTED WITH THE  
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*For Each Patent That Claims a Drug Substance  
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NDA NUMBER  
21-446  
NAME OF APPLICANT / NDA HOLDER  
Parke-Davis, Division of Pfizer Inc

*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)  
Lyrica

ACTIVE INGREDIENT(S)  
Pregabalin  
s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid

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Oral Capsules

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**1. GENERAL**

a. United States Patent Number 6,001,876	b. Issue Date of Patent 12/14/1999	c. Expiration Date of Patent 7/16/2017
d. Name of Patent Owner Warner-Lambert Company LLC Attn: Charles Ashbrook, Esq. 2800 Plymouth Road Ann Arbor, Michigan 48105	Address (of Patent Owner) 201 Tabor Road	
	City/State Morris Plains, New Jersey	
	ZIP Code 07950	FAX Number (if available) 734-622-1553
	Telephone Number 734-622-5215	E-Mail Address (if available)
e. <u>Name of agent or representative</u> 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)  <input type="checkbox"/> N/A	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? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> 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) 1, 2, 3, 5 and 13 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 1, 2, 3, 5 and 13 all claim the treatment of pain generally, or the treatment of neuropathic pain or acute herpetic and postherpetic pain specifically, using pregabalin or a compound selected from a genus of compounds that includes pregabalin. Claims 1 and 2 are directed to the treatment of pain using a compound selected from a genus of compounds that includes pregabalin. Claim 3 is directed to the treatment of pain using pregabalin. Claim 5 is directed to the treatment of neuropathic pain using a compound selected from a genus of compounds that includes pregabalin. Claim 13 is directed to the treatment of acute herpetic and postherpetic pain using a compound selected from a genus of compounds that includes pregabalin.

**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

Appears This Way  
On Original

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.

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

*Karen DeBenedictis* 10/2/03

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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 Karen DeBenedictis	
Address Pfizer Inc 2800 Plymouth Rd.	City/State Ann Arbor, Michigan
ZIP Code 48105	Telephone Number 734-622-3374
FAX Number (if available) 734-622-2928	E-Mail Address (if available) Karen.DeBenedictis@pfizer.com

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EXCLUSIVITY SUMMARY FOR NDA # 21-446, 21-723\_\_ SUPPL #\_\_\_\_\_

Trade Name LYRICA\_\_\_\_\_ Generic Name pregabalin\_\_\_\_\_

Applicant Name Pfizer Gloval Research and Development  
HFD #170\_\_\_\_\_

Approval Date If Known \_\_\_\_\_

**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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
YES /\_X\_/ NO /\_\_\_/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

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 /\_X\_/ 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:

d) Did the applicant request exclusivity?

YES /X/ NO /\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

five \_\_\_\_\_

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /X/

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?

---

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 /X/

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 /X\_/

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

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 NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ 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 /\_\_\_/

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:

---

---

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.")



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 !  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
! !  
!

Investigation #2 !  
IND # \_\_\_\_\_ 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?

Investigation #1 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! !  
! !  
! !  
! !

Investigation #2 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ 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: \_\_\_\_\_  
\_\_\_\_\_

Signature  
Title:

Date

Signature of Office/  
Division Director

Date

Form OGD-011347 Revised 05/10/2004

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/s/

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Robert Meyer  
12/30/04 03:34:11 PM

## PEDIATRIC PAGE

DA/BLA #: 21-446 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

App Date: October 31, 2003 Action Date: July 31, 2004 (following review clock extension)

FD-170 Trade and generic names/dosage form: LYRICA (pregabalin)/capsule

Applicant: Pfizer Global Research & Development Therapeutic Class: P1

Indication(s) previously approved: \_\_\_\_\_ None

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

Number of indications for this application(s): 1

Indication #1: Pain associated with diabetic peripheral neuropathy

Do you have 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 comment 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. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ 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: \_\_\_\_\_

*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. \_\_\_\_\_ 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 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:

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

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/s/

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Lisa Malandro  
6/4/04 11:22:34 AM

**Office Director's Sign-Off Memorandum**

Date: Thursday, December 30, 2004  
NDA: 21-446, 21-723  
Sponsor: Pfizer  
Proprietary Name: LYRICA (Pregabalin) Capsules  
From: Robert J. Meyer, MD  
Director, ODE II

---

**Introduction:** This is the final sign off memorandum for LYRICA (pregabalin), a new molecular entity, now on its second cycle of review. See my previous memorandum of July 28<sup>th</sup>, 2004 to NDA 21-446 and August 31<sup>st</sup>, 2004, to NDA 21-723 for full details. Of note, the main issue precluding approval in the previous cycle was disagreement on the scheduling of LYRICA. The controlled substances staff and NIDA had recommended scheduling as a C-IV, but Pfizer believes their data do not show significant abuse potential. After an appeal to the Office of the Center Director, FDA is moving forward with recommending of scheduling, although it is not clear at this point if that recommendation will be a schedule IV or V. Pfizer is now accepting that the drug will be recommended for scheduling by FDA.

It should also be noted that due to issues of timing (priority vs. non-priority reviews), this NDA was administratively separated. ☐

1

Save for issues of scheduling, all other issues have been resolved with LYRICA, including adequate labeling.

**Regulatory Conclusions:**

Since Pfizer is no longer contesting an approval prior to the scheduling being finalized, LYRICA should be approved for use in the treatment of pain associated with diabetic peripheral neuropathy and for the treatment of post-herpetic neuralgia. In addition to the previous phase 4 commitments, we will need a commitment from the sponsor to not market the product until scheduled and at that time, we will need to have a CBE labeling supplement for addition of the scheduling information.

Robert J. Meyer, MD  
Director,  
Office of Drug Evaluation II

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**This is a representation of an electronic record that was signed electronically and  
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/s/

-----  
Robert Meyer  
12/30/04 03:51:09 PM  
MEDICAL OFFICER

Michigan Laboratories  
Pfizer Inc  
2800 Plymouth Road  
Ann Arbor, MI 48105



30 December 2004

## Global Research & Development

Russell G. Katz, MD  
Division Director  
Division of Neuropharmacological  
Drug Products (HFD-120)  
Document Control Room 4037  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Woodmont Office Complex II  
1451 Rockville Pike  
Rockville, MD 20852

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Bob Rappaport, MD  
Division Director  
Division of Anesthetic, Critical Care  
and Addiction Drug Products (HFD-170)  
Attn: Division Document Room, 8B-45  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Parklawn Building  
5600 Fishers Lane  
Rockville, MD 20857

*11/11/04*  
*20857*  
*AM 12/30/04*

Dear Drs. Rappaport and Katz:

**RE: General Correspondence**

**Lyrica™ (pregabalin) Capsules**  
**NDA 21-446 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy**  
**NDA 21-723 Neuropathic Pain Associated with Postherpetic Neuralgia**  
**NDA 21-724 Adjunctive Epilepsy Therapy**

1

**ELECTRONIC SUBMISSION**  
**1 CD-ROM, ~ 300 KB**  
**Reference No. - 0081**

Drs. Rappaport and Katz  
NDA 21-446  
30 December 2004  
Page 2

Reference is made to our New Drug Application for Lyrica™ (pregabalin) Capsules, NDAs 21-446, 21-723, 21-724 submitted on 30 October 2003 filed with the Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP). Further reference is made to the 01 November 2004 resubmissions for NDA 21-446 and NDA 21-723.

In response to the recent interactions with DACCADP, this letter seeks to formalize the previous communications, supply the FDA with the requested material and provide the Agency with an update of our position regarding the abuse potential for pregabalin.

It is our expectation that CDER will be recommending Lyrica to be classified as Schedule V under the Controlled Substance Act. We recognize that the full scheduling process is ongoing and will not be completed prior to approval. Pfizer agrees not to market Lyrica until a final decision has been communicated.

Pfizer acknowledges and commits to the post-approval commitments requested by FDA. Pfizer proposes the following timelines for these commitments.

1. Complete an adequate and well-controlled clinical study to assess the effect of pregabalin on nerve conduction velocity (NCV)

Protocol Submission: *by 21 April 2004\**  
\*The final protocol has been agreed with FDA.  
Study Start: *by 1 September 2004\**  
\*This study has already started.  
Final Report Submission: *by March 2006*

2. Complete an in vitro study of the propensity of pregabalin to induce CYP-enzyme metabolism

Protocol Submission: *by February 2005*  
Study Start: *by March 2005*  
Final Report Submission: *by December 2005*

3. Complete an adequate and well-controlled clinical study or studies to better assess the ophthalmologic toxicity of pregabalin

Protocol Submission: *by August 2005\**  
\*Reflects dialogue with external and FDA experts to achieve a draft protocol for final FDA agreement.  
Study Start: *by July 2006*  
Final Report Submission: *by January 2009*

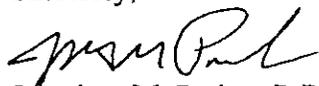
Drs. Rappaport and Katz  
NDA 21-446  
30 December 2004  
Page 3

This submission is comprised of 1 CD-ROM. In addition, a hard copy of the table of contents outlining the specific information included with this submission is being provided. The CD-ROM has been scanned with McAfee Data Pack Version 4.2.60 with Virus Definition Pack Version 4.0.4312 and is virus free.

Pfizer, Inc respectfully requests that this information be included in our file for NDAs 21-446, 21-723, 21-724, and 21-725 and be forwarded to the Controlled Substance Staff (CSS).

If you have any questions regarding this submission, please do not hesitate to contact me at (734) 622-5377 or via facsimile at (734) 622-2856.

Sincerely,



Jonathon M. Parker, R.Ph., M.S.  
Global Regulatory Leader  
Regulatory Strategy  
Worldwide Regulatory Affairs

Enclosure (1 CD-ROM)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT C.P Pharmaceuticals International C.V.	DATE OF SUBMISSION 30 December 2004
TELEPHONE NO. (Include Area Code) (212) 573-4471	FACSIMILE (FAX) Number (Include Area Code) (212) 857-3558
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): c/o Pfizer Inc. 235 East 42 <sup>nd</sup> Street New York, NY 10017 Att: David Reid, Manager, C.P. Pharmaceuticals Int'l C.V.	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Pfizer Inc. 2800 Plymouth Road Ann Arbor, Michigan 48105

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-446		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Pregabalin	PROPRIETARY NAME (trade name) IF ANY Lyrica	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (S)-3-(aminomethyl)-5-methylhexanoic acid	CODE NAME (if any) CI-1008, PD 0144723	
DOSAGE FORM: Capsules	STRENGTHS: 25, 50, 75, 100, 150, 200, 225, and 300 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Neuropathic Pain, [ ]		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)	
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER	
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____	
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)	

REASON FOR SUBMISSION

Commitment Letter
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 49,393, IND 53,763, IND [ ] NDA 21-723, NDA 21-724, [ ]

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index - Electronic and Paper
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Commitment Letter

**CERTIFICATION**

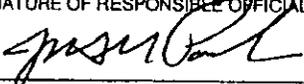
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Jonathon M. Parker, RPh, MS, Global Regulatory Leader	DATE: 30 December 2004
ADDRESS (Street, City, State, and ZIP Code) 2800 Plymouth Road, Ann Arbor, Michigan 48105		Telephone Number (734) 622-5377

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12/22/04

**NDA 21-446**

**LYRICA (pregabalin) Capsules, 25, 50, 75, 100 mg**

**CHEMISTRY DIVISION DIRECTOR REVIEW #4**

**Applicant:**

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, MI

**Indication:** Neuropathic Pain

**Presentation:** blisters 4 X 6 capsules/card, and 90 count HDPE bottles (a 500 count bottle is approvable and will be introduced post approval)  
Physician samples 30 & 45 count in 45 mL HDPE bottles

**EER Status:** Acceptable 22\_JUN\_2004

**Consults:** DMETS – Tradename: LYRICA - acceptable 15-MAR-2004  
Statistics – drug substance re-test/addnl data subsequently provided  
EA – no consult - waiver requested – granted

**Post Approval Agreements:**

The first 3 lots of drug substance manufactured at the  
Ringaskiddy IRE facility using [ ] will be tested for  
[ ]

The drug substance bulk density specification will tentatively be not less than — mL, and additional data will be gathered and the specification revised to not less than — mL if supported by the additional commercial scale batch data and will be reported in the 1<sup>st</sup> annual report.

The original NDA was received 30-OCT-2003

[ ] }  
[ ] }  
[ ] }  
[ ] }

Note that an amendment submitted 30-AUG-2004 will not be reviewed in this review cycle.

The **drug substance** is manufactured by:

Pfizer Ireland, Inc.  
Ringaskiddy, IRE

Manufacturing and controls information was reviewed and were found acceptable. Of note was the issue of the potential carcinogenic impurity [redacted] which could be formed during [redacted] of the drug substance from [redacted]. Data were provided from the analyses of [redacted] batches for [redacted] and none was detected. The level of quantitation was [redacted] ppm. This is considered adequate. No controls for this potential impurity are considered needed. A [redacted] process was proposed so a phase 4 commitment was made to test the first 3 lots of drug substance manufactured at the Ringaskiddy IRE facility using [redacted]. Comparability protocols providing for alternate starting materials and manufacturing processes were found acceptable following the establishment of added controls. The alternate manufacturing protocols provide, [redacted]

[redacted] Structural alerts for mutagenicity are present for various [redacted]. [redacted] controls were required to be established. The added controls along with [redacted] as compared with the [redacted] character of pregabalin renders [redacted] in the [redacted] pregabalin [redacted] highly effective.

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. A re-test period of [redacted] was requested, and is supported by 36 months submitted stability data on only pilot scale batches from the R&D site – a [redacted] re-test is granted. The stability testing protocol is considered adequate.

#### **Conclusion**

Drug substance is satisfactory.

The **drug product** is capsules of 25, 50, 75, 100 mg.

Manufacturer:

Parke Davis, Div Warner Lambert Co.  
Vega Baja, PR

The manufacturing method is [redacted] process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The

submitted stability data are adequate to support the requested 36 month expiry in all presentations. The stability testing protocol is considered adequate. The established name pregabalin is USAN.

Labeling is acceptable.

The overall Compliance recommendation is acceptable as of 22-JUN-2004.

All associated DMFs are acceptable

**Overall Conclusion**

From a CMC perspective the application is recommended for approval.

Eric P Duffy, PhD  
Director, DNDC II/ONDC

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  ✓   § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> October 9, 2003	<b>DESIRED COMPLETION DATE:</b> December 9, 2003	<b>ODS CONSULT #:</b> 03-0282
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**TO:** Russell Katz, MD  
Director, Division of Neuropharmacological Drug Products  
HFD-120

**THROUGH:** Richardae Taylor, PharmD  
Project Manager  
HFD-120

<b>PRODUCT NAME:</b> Lyrica™ (Pregabalin Capsules) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg	<b>IND SPONSOR:</b> Parke-Davis Pharmaceutical Research, Division of Pfizer, Inc.
---	--

**IND#:** —

**SAFETY EVALUATOR:** Kimberly Culley, RPh

**RECOMMENDATIONS:**

- DMETS has no objections to the use of the proprietary name, Lyrica™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name Lyrica™ acceptable from a promotional perspective.

**/S/**

**/S/**

Carol Holquist, RPh  
Deputy Director,  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242      Fax: (301) 443-9664

Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 10, 2003  
IND# [ 7  
NAME OF DRUG: Lyrica™ (Pregabalin Capsules) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg  
IND HOLDER: Parke-Davis Pharmaceutical Research, Division of Pfizer, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the proprietary name, "Lyrica™", regarding potential name confusion with other proprietary or established drug names. Draft container labels and package insert labeling were provided for review and comment.

PRODUCT INFORMATION

Lyrica™ is the proposed proprietary name for pregabalin. Parke-Davis Pharmaceutical Research has proposed three indications for pregabalin including management of neuropathic pain, [

capsules will be available in strengths of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. ] Lyrica™

The recommended dose and dosage range is dependent upon indication. For the management of neuropathic pain, the recommended starting dose for pregabalin is 75 mg twice daily with efficacy noted in a range of 150 mg per day [ ] The maximum dose is 300 mg [

] [

] ]

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Lyrica™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Trademark Electronic Search System (TESS)<sup>4</sup> was also conducted. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Lyrica™. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed name, Lyrica™, acceptable from a promotional perspective.
2. The Expert Panel identified four (4) proprietary names that were thought to have the potential for confusion with Lyrica™. These products are listed in table 1 (see page 4), along with the dosage forms available, strengths available and usual dosage.

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<sup>1</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>4</sup> US Patent and Trademark Office with a WWW location of <http://tess2.uspto.gov/bin/gate.exe?f=tess&state=iujsak.1.1>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s), Available strengths	Usual adult dose	Other**
Lyrica™	Pregabalin, Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg	Neuropathic pain 75mg twice daily (BID)	
Cycrin®	Medroxyprogesterone acetate, Tablets 2.5 mg, 5 mg, 10 mg	5 to 10 mg daily (QD) for 5 to 10 days	Look-alike
Lupron®	Leuprolide, Injection 3.75 mg, 5 mg ml, 7.5 mg, 11.25 mg, 22.5 mg, 30 mg, 72mg	Injection: 5mg/ml, 1mg subcutaneously (SC) QD Dosage for intramuscular (IM) depot is varying for different indications Depot: 3.75mg, 7.5mg (monthly) Depot-Ped: 7.5mg, 11.25mg, 15 mg (monthly) Depot 3: 11.25mg, 22.5mg (every three months) Depot 4: 30mg every four months Implant: 72mg every 12 months	Look-alike
Lasix®  Furosemide, generic	Furosemide, Tablets 20 mg, 40 mg, 80 mg, Furosemide, Oral solution 10 mg/mL Furosemide, Injectable 10mg/mL  Furosemide, oral solution 40 mg/5 mL	Edema: 20 to 80 mg/day as a single dose Hypertension: 40 mg BID	Look-alike
Luride®	Fluoride, Tablets 0.25 mg (0.55 mg sodium fluoride (NaF)), 0.5 mg (1.1 mg NaF), 1 mg (2.2 mg NaF)  Fluoride, Drops 0.5 mg/mL (1.1 mg NaF)	Prevention of dental caries; varies by age and content of fluoride in drinking water. Highest possible dose below for fluoride level < 0.3 ppm 6 mos- 3 years: 0.25mg per day 3 to 6 years: 0.5mg per day 6-16 years: 1 mg per day	Look-alike
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

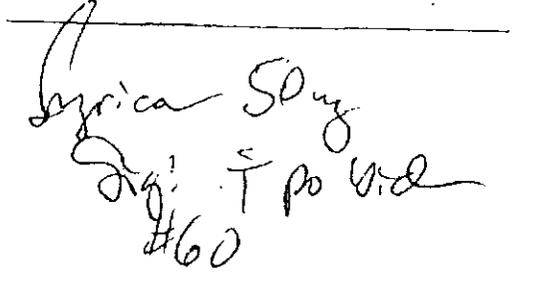
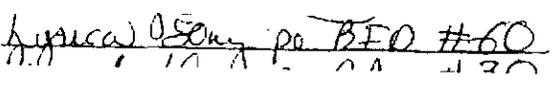
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lyrica™ with marketed U.S. drug

names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 77 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Lyrica™ (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p>  <p>Lyrica 50mg qd #60</p>	<p>Lyrica 50mg One twice daily Number 60</p>
<p>Inpatient RX:</p>  <p>Lyrica 50mg po BID #60</p>	

## 2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. Among the written *inpatient* responses, the primary discrepancy included the misinterpretation of the letter “L” for “S” (e.g. Syrica). However, one participant from the written outpatient study commented on the possibility for confusion with the recently approved drug, Levitra®. However, this participant did provide an alternate interpretation of the Lyrica™ prescription. See appendix A for the complete listing of interpretations from the verbal and written studies.

## E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Lyrica™, the primary concerns related to look-alike confusion with Cycrin®, Lupron®, Lasix® and Luride®. Upon further review of the names gathered from EPD, independent analysis and POCA, the names Luride® and Lasix® were not reviewed further due to a lack of convincing look-alike similarities with Lyrica™ in addition to numerous differentiating product characteristics such as the patient population, product strength, indication for use, frequency of administration and dosage formulations.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with

any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Lyrica™. Of note, one participant remarked on the possibility for sound-alike confusion with Lyrica™ and Levitra®, which will be reviewed in depth below.

1. Sound-alike and or look-alike concerns

- a. Cycrin® looks similar to Lyrica™ when scripted. Although Cycrin® is no longer marketed, there is a familiarity with this proprietary name and a common practice of generic substitution. Due to this practice, there is continued concern with potential name confusion. Cycrin® contains medroxyprogesterone acetate and is indicated for use in amenorrhea and abnormal uterine bleeding. The potential name confusion can be primarily attributed to certain similarities of the two names when written in cursive. These similarities include the resemblance of capitalized “C” and “L”, the shared “y” letter in the first syllable, and the resemblance of “cr” and “r” when scripted (see below). In addition, cursive handwritten orders tend to taper off obscuring the identity of the last letters, which may diffuse the power of the distinctive endings of “n” and “a” (of Cycrin® and Lyrica™, respectively).



The image shows two handwritten words in cursive: 'Cycrin' on the left and 'Lyrica' on the right. The 'C' in 'Cycrin' and the 'L' in 'Lyrica' are written in a very similar, rounded, looped style. The 'y' in both words is also written in a similar, elongated cursive style. The overall appearance of the two words when written quickly is quite similar, illustrating the potential for confusion mentioned in the text.

Although there are no obvious strength or dosing overlaps, decimal points are often missed and zeros often misinterpreted when writing and reading prescriptions. This may lead to concern regarding three particular strengths of the two products. Cycrin® is available as 2.5 mg, 5 mg and 10 mg tablets with Lyrica™ available in 25 mg, 50 mg and 100 mg capsules. Post-marketing experience has shown errors occurring between products that share numerically similar strengths or doses. This potential strength confusion may be precluded by differences in dosing frequency (daily for Cycrin® versus twice daily for Lyrica™). However, due to the nature of this medication, there will be circumstances where Lyrica™ may be dosed daily. One such instance of particular concern would involve patients with renal dysfunction who could receive Lyrica™ dosed at 25 mg daily that has the potential for confusion with Cycrin® 2.5 mg daily. This could also translate to the 50 mg and 100 mg strengths of Lyrica™ with the 5 mg and 10 mg strengths of Cycrin® that would be of concern if the doses were written with trailing zeros (e.g. 5.0 vs. 50 mg). Dose and strength confusion may be alleviated by the typical day supply prescribed. Cycrin® is customarily prescribed daily for five to ten days per month in contrast to the daily or twice daily for a thirty day supply of Lyrica™. Furthermore, the medications have different indications and potentially different prescriber groups. Despite similarities when scripted, the differences in standard dosing frequencies, strengths and duration of treatment minimize the risk of confusion between Cycrin® and Lyrica™.

- b. Lupron® looks like Lyrica™ when written. Lupron contains leuprolide acetate and is indicated for use in advanced prostatic cancer, endometriosis, uterine leiomyomata and central precocious puberty. Lupron® is an injectable product administered by subcutaneous and intramuscular route. The confusion between the products can be

primarily attributed to the shared letters including the leading “L” and subsequent “r” and a resemblance of the letters “up” versus “y” when written in cursive in Lupron® and Lyrica™, respectively. The names are also similar in character length (see below). Moreover, cursive handwritten orders tend to taper off obscuring the identity of the last letters.

The image shows two handwritten cursive words side-by-side. The word on the left is 'Lupron' and the word on the right is 'Lyrica'. Both words are written in a fluid, cursive style that tapers off at the end, making the final letters less distinct.

There is potential for error with overlapping strengths if confusion or a misinterpretation of the decimal point occurs. Post-marketing experience has shown errors occurring between products that share numerically similar strengths or doses. For these products, the dosages of interest include 7.5 mg versus 75 mg and 5 mg versus 50 mg for Lupron® and Lyrica™, respectively. However, DMETS believes there is minimal risk for error between the two drugs for multiple reasons including differing administration routes (injectable versus oral), dosage forms, dosage frequencies (monthly versus daily/twice daily), doses, drug storage and patient populations. In addition, the subcutaneous formulation of Lupron® (available as 5 mg/mL) that can be administered daily is stored in the refrigerator and will typically be dosed as 1 mg daily. Although, a possibility for name confusion exists, the significant difference in administration route, storage and dosage regimen should help reduce error and misinterpretation.

- c. Levitra® sounds similar to Lyrica™. This was noted by a participant in the prescription studies, although the participant did provide another interpretation of the name. Levitra® contains vardenafil hydrochloride and is indicated for the treatment of erectile dysfunction. Upon observation, the similarity appears to be mnemonic in nature. The rhyming names and possible corresponding similarities in inflection could be of concern. The three syllables in both product names can yield to similarity for various reasons. The “y” in the first syllable for the proposed name, Lyrica™ can be pronounced in multiple ways (ī, ĩ, ỹ, etc) as a result of differing dialects and interpretations of the name. Furthermore, both names end with an “□” sound, although spelled differently as “ca” and “tra”. This suggests possible confusion on verbal prescription orders due to the distinctive, but similar tonal beginning and endings. To add to confusion, the middle syllables “vi” versus “ri” can be comparable in pronunciation. However, the markedly differing indications, dosing regimens, strengths, and patient populations may deter confusion. The average Levitra® patient will receive the product as an as needed medication, not as a maintenance medication which is in opposition to Lyrica™ patients. Levitra® is available in 2.5 mg, 5 mg, 10 mg and 20 mg strengths, therefore no overlap with Lyrica™ for verbal orders. Due to the above mentioned differences, DMETS believes there is minimal risk for confusion between Levitra® and Lyrica™.

2. Concern with overlapping strengths and capsule colors

The proposed 25 mg, 50 mg and 150 mg capsule color is presently documented as white. There is concern over distinguishing between the dosages. DMETS acknowledges the text contents will be marked on each capsule (e.g. PBN 100), but this may be overlooked by health care providers and patients. Thus, we encourage the capsules will be distinctive by varying capsule size or different color codes.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels of Lyrica™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

#### A. CONTAINER LABEL

1. Please include the dosage form "capsule" in the established name "pregabalin."
2. The net quantity statement of "60 capsules" is equally as prominent as the statement of strength of 100 mg on the green background. Consider decreasing font size for the capsule count to diminish potential confusing with strength.
3. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 60 capsule size) in accordance with the Poison Prevention Act.

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**IV. RECOMMENDATIONS:**

- A. DMETS has no objections to the use of the proprietary name, Lyrica™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Lyrica™ acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

*/s/*

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Kimberly Culley, RPh  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

*/s/*

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Alina Mahmud, RPh  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Inpatient	Outpatient	Voice
Lyrice	Filirika	Lyrice
Lyrice	Lankin	Lyrice
Lyrice	Learice	Lyrice
Lyrice	Leirice	Lyrice
lyrice	Lereca	Lyrice
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Carol Holquist  
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**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** November 23, 2004

**TO:** Bob Rappaport, M.D., Director  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

**VIA:** Lisa Malandro, Regulatory Health Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M. D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCs Review #2 of Patient Labeling for Lyrica (pregabalin)  
Capsules Capsules, NDAs 21-446 and 21-723

**Summary**

The patient labeling which follows represents the revised risk communication materials of the Patient Package Insert (PPI) for Lyrica (pregabalin) Capsules, NDAs 21-446 and 21-723. We have made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on revised draft labeling submitted November 1, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

We also have the following comments:

1. The Patient Information Subcommittee (PISC) determined that pregabalin meets the criteria for a MG for pregabalin (April 12, 2004) because of the serious and significant public health concern of vision changes associated with the product.

2. If the review division considers it important for a patient to receive written information, a Medication Guide should be considered instead of a PPI. Medication Guides are required to be given to the patient when an outpatient prescription is dispensed. PPIs are voluntary and are unlikely to be given to patients unless they are printed, packaged, and dispensed in unit-of-use packages with the drug product. The sponsor states in the PI, PRECAUTIONS section, Information for patients subsection, "Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA." However, the sponsor has not provided information on how the patient is going to receive this voluntary PPI. Unless the sponsor has a plan for printing and distributing the PPIs to patients, the statement referencing the PPI should be deleted from the PI. Patients usually receive pharmacy-generated patient information with their prescriptions. Pharmacy-generated written patient information would not be an acceptable substitute for the FDA-approved Lyrica PPI. Various vendors independently create pharmacy printouts, otherwise known as consumer medication information (CMI). There are no content requirements for CMI, which could vary greatly from the approved Lyrica PPI. The 2001 Evaluation of Written Prescription Information Provided in Community Pharmacies<sup>1</sup> found that the quality of CMI varied widely, with ratings especially low on criteria dealing with the risks of drug treatment and general information. CMI is not regulated by the Agency.
3. If the product is Scheduled as recommended, include the appropriate information in the PPI for the patient. The sponsor has alluded to physical dependence /withdrawal symptoms in both the PI (PRECAUTIONS section, Abrupt or rapid discontinuation) and PPI (How do I take LYRICA? Section "Do not suddenly stop taking LYRICA. Talk with your doctor about how to stop LYRICA."). The sponsor does not tell the patient the reason, nor list symptoms, if the patient suddenly stops the drug product. If the reasoning behind these statements is physical dependence/withdrawal symptoms, then this information should be added to the PI and PPI.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

## PATIENT INFORMATION

**LYRICA** (LEER-ik-ah)  
**PREGABALIN**

<sup>1</sup> Fir... Department Of Health and Human Services and the Food and Drug Administration; Svarstad and Mount; University Of Wisconsin at Madison, School of Pharmacy, 2001

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Jeanine Best  
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Toni Piazza Hepp  
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DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

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\_\_\_\_\_ § 552(b)(5) Draft Labeling

## MEMORANDUM OF TELECONFERENCE

DATE: November 3, 2004

APPLICATION NUMBER: NDA 21-446, LYRICA (pregabalin) Capsules

BETWEEN:

Name: Pfizer, Inc.,

AND

Name: Eric Duffy, Director, Division of New Drug Chemistry II  
Ravi Harapanhalli, Chemistry Team Leader  
Lisa Malandro, Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Acceptability of launch materials

In a brief teleconference held on November 3, 2004, representatives of Pfizer were informed that it is acceptable with the Agency for them to use pre-printed launch materials. These launch materials were printed with the incorrect presentation of the established name as LYRICA (pregabalin) omitting the word "Capsules." Pfizer agreed that, at the time of the next printing, all materials would be printed with the established name "LYRICA (pregabalin) Capsules.

Pfizer was also reminded that the launch materials would have to be reprinted if the Agency recommended that the drug be scheduled under the Controlled Substance Act.

/s/

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Lisa Malandro  
Regulatory Project Manager

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Lisa Malandro  
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## MEMORANDUM OF TELECONFERENCE

DATE: October 4, 2004

APPLICATION NUMBER: NDA 21-446, LYRICA (pregabalin) Capsules

BETWEEN:

Representatives of Pfizer Inc.,

AND

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

Name: Robert Meyer, MD  
Bob Rappaport, MD  
Celia Winchell, MD  
Mwango Kashoki, MD  
Thomas Permutt, PhD  
Joan Buenconsejo, PhD  
Ling Chen, PhD  
Sue-Chih Lee, PhD  
Lisa Malandro, Regulatory Project Manager

Division of Neuropharmacological Drug Products; HFD-120

Alicc Hughes, MD  
John Feeney, MD

SUBJECT: Labeling meeting

A teleconference was held on October 4, 2004, in order to discuss the current draft label for NDA 21-446, 21-723, ☐

3. Items that were unresolved at the time of the regulatory actions were discussed so that the Sponsor was aware of the Agency's reasoning and could address Agency concerns in their resubmissions.

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Lisa Malandro  
Regulatory Project Manager

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/s/

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Lisa Malandro  
12/22/04 05:31:55 PM  
CSO

**Malandro, Lisa**

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**From:** Malandro, Lisa  
**Sent:** Thursday, October 07, 2004 3:09 PM  
**To:** 'Bammert, James'; Malandro, Lisa  
**Cc:** Parker, Jonathon M (Regulatory Affairs)  
**Subject:** RE: Lyrica name on carton/containers

Jim,

The chemists have the following comment regarding the presentation of the established name on the carton/container labels:

The established name is "LYRICA (pregabalin) Capsules" and this should be included in the labeling (both PI and container/carton labels). Your proposal to delete "Capsules" is unacceptable.

Please contact me if you have any questions.

Thanks,  
Lisa

-----Original Message-----

**From:** Bammert, James [mailto:James.Bammert@pfizer.com]  
**Sent:** Wednesday, October 06, 2004 9:29 AM  
**To:** 'Lisa Malandro (E-mail)'  
**Cc:** Parker, Jonathon M (Regulatory Affairs)  
**Subject:** RE: Lyrica name on carton/containers

isa,

any news on this question? Thanks.

im

-----Original Message-----

**From:** Bammert, James  
**Sent:** Wednesday, September 29, 2004 6:05 PM  
**To:** Lisa Malandro (E-mail)  
**Cc:** Parker, Jonathon M (Regulatory Affairs)  
**Subject:** Lyrica name on carton/containers

Lisa,

Hi, how is it going? Were you able to find out about the tradename on carton/container labels as referenced in the Approvable letters?

"Lyrica (pregabalin)" instead of "LYRICA (pregabalin) Capsules"

Thanks

Jim

Jim Bammert, R.Ph.  
Manager  
Worldwide Regulatory Affairs and Quality Assurance  
(WRAQA)

> Pfizer Global Research & Development  
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>  
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"MMS <secure.pfizer.com>" made the following annotations on 10/06/2004 09:29:19 AM

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Lisa Malandro  
10/7/04 03:11:37 PM

9/1/04

**DISPUTE RESOLUTION ISSUES  
RELATED TO PREGABALIN, ITS ABUSE LIABILITY  
AND CSA SCHEDULING**

**I. Executive Summary**

Pfizer's request for dispute resolution relative to the CSS abuse liability assessment and possible Controlled Substances Act (CSA) scheduling of pregabalin focuses on an "abuse signal" that comes from clinical trial data and human pharmacology study results submitted in the New Drug Application (NDA). The CSS assessment of the "abuse signal" discusses the following:

- The appearance of a high rate of "euphoria" and other CNS abuse-related adverse events in clinical trials,
- The results of a human laboratory abuse study that compared pregabalin to diazepam, and
- The contention that pregabalin is similar to the nonscheduled gabapentin and thus not likely to be abused.

The sponsor to a large extent dismisses the significance of the "abuse signal" and the studies where the signal appeared. For example, draft labeling for the product submitted by Pfizer in August 2004 include the following statement in the DRUG ABUSE AND DEPENDENCE section in referring to the results of the human laboratory abuse liability study:

[ ]

The sponsor may find this selective dismissal of scientific evidence to be convenient.

Similarly, relative to the high rates of "euphoria" reported in clinical trials, Pfizer argues that "euphoria" is not a good indicator of abuse liability. According to the sponsor, "euphoria" reports by patients taking pregabalin in clinical trials for the treatment of Generalized Anxiety Disorder (GAD) occurred at the following rates: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. Of marketed drugs, only the cannabinoid, dronabinol (Marinol), which is controlled in Schedule III of the CSA, had a comparable incidence of euphoria (3% to 10%) in clinical trials.

The CSS analysis of the individual patient data in the GAD, epilepsy and neuropathic pain efficacy trials produced the following: 6.1 - 6.8% of all patients experienced a CNS adverse event associated with drugs of abuse (see Table 1 below, and discussion on pages 5 and 6). Of those patients who experienced such an adverse event, 53-71% experienced multiple incidents of those adverse events. Between one-third to one-half of patients who reported euphoria in clinical trials were discontinued from study, which might explain why reports of euphoria decreased with time.

Table 1. Incidence of Euphoria and other CNS Abuse-Related Adverse Events.

Patients by Clinical Trial	Euphoria**	Other CNS Abuse-Related AEs ***	Total
GAD Patients * (N = 1149)	29	41	70
% of 1149	2.5%	3.7%	<b>6.1%</b>
Epilepsy Patients (N = 758)	12	37	49
% of 758	1.6%	4.9%	<b>6.5%</b>
Pain Patients (N = 1831)	37	88	125
% of 1831	2.0%	4.8%	<b>6.8%</b>

\*Study 1008-088, which had an open label enrichment phase prior to the double-blind phase, tested only 450 mg pregabalin: 19 of 168 patients (11.3%) had an adverse event associated with a drug of abuse. This approximates the 11.8% rate of euphoria shown in Pfizer-submitted tables for the 450 mg dose of pregabalin.

\*\* "Euphoria" includes: high, stoned, elation, elevated mood, intoxicated, increased well-being, excessive happiness, drugged, drunk, giddy, mood swings, hallucinations, floating, feeling addicted.

\*\*\* Drug effect known to be associated with other drugs of abuse: decreased concentration, disoriented, decreased memory, lightheaded, spacey, confusion, mental slowing, groggy, stupor, woozy, muzzy, mental disturbance, delirious, disconnected, derealization, dissociation, detached, depersonalization, psychomotor stimulation, jittery, edgy.

Pfizer's viewpoint relative to the incidence of euphoria in clinical trials is based on their perception of the experience from unscheduled drugs (for example, bupropion and olanzapine), which also produced euphoria in clinical trials. Review of the clinical trial data reported in the product label for bupropion reveals, however, that the rate of euphoria for bupropion was 1.2%, which is identical to that of euphoria for placebo in the GAD trials with pregabalin. Similarly, the label for olanzapine lists euphoria as a "frequent" adverse event, though the "frequent" rate is defined to be occurring in at least

1/100 patients. In contrast, zolpidem and zaleplon, which are not benzodiazepines though they produce CNS depressant effects and benzodiazepine-like subjective effects, were each placed into Schedule IV of the Controlled Substances Act. Their product labels list the occurrence of euphoria in a wide range of frequencies, in greater than 1/100 patients for zolpidem (rated frequent) to a range of less than 1/100 patients but more than 1/1000 patients for zaleplon (rated infrequent).

Pfizer also maintains that a lack of dose escalation in the open label trials demonstrates that the euphoria response was not adequate to maintain drug-seeking in patients. Similarly, Pfizer concludes that patients who experienced euphoria did not choose to enter open label trials more frequently than those patients who did not experience euphoria, though an analysis in support of this conclusion was not submitted for Agency review. After a reporting of euphoria, many subjects were discontinued from study.

In order to interpret the "abuse signal" for pregabalin, it is necessary to place euphoria data from clinical trials in the context of other abuse-related data, such as the human abuse study. For zolpidem and zaleplon, human laboratory abuse potential studies showed that these drugs produced positive subjective responses that were similar to other Schedule IV benzodiazepines. Thus, zolpidem and zaleplon were placed into Schedule IV, despite low incidences of euphoria, because of a strong signal from a human laboratory study. In contrast, bupropion produced positive subjective responses that were intermediate between placebo and the comparator drug, amphetamine, as well as a low euphoria. Thus, bupropion was marketed as an unscheduled drug because its abuse liability signals were weak from two sources.

When the high rate of euphoria from clinical trials with pregabalin is assessed in the context of the strong abuse liability signal from pregabalin in the human laboratory abuse liability study, as described below, the overall picture is that pregabalin has an abuse liability similar to other scheduled drugs, thus warranting CSA scheduling. Because of similar results in the human abuse study with compared to diazepam, Schedule IV seems appropriate, though the high rate of euphoria from pregabalin, especially at the 450 mg dose, raises additional concerns.

The human laboratory abuse liability study involved subjects experienced in the recreational use of sedatives and alcohol. Primary measures of abuse liability were "good drug effect," "high," "liking," and "liking (end of session)." Responses were similar to and sometimes greater than the responses following administration of 15 and 30 mg diazepam, the Schedule IV active control. A statistical analysis of the individual data shows that diazepam is significantly different from placebo on the primary subjective measures, thus validating the study. Further statistical analysis shows that pregabalin does not have a statistically lower mean response on these primary measures than diazepam, nor does pregabalin have a statistically lower mean response than double the mean response of placebo. Thus, the statistical analysis of the study fails to show that

pregabalin has no abuse liability, but rather that the abuse potential of pregabalin is similar to that of diazepam. Additionally, the CSS analysis included review of all secondary outcome measures and these are discussed below.

The Sponsor weakly argues that the delayed time to peak of positive subjective effects makes pregabalin significantly different from diazepam. However, other drugs that have delayed onset times are scheduled. For example, the Schedule I hallucinogen DOM (4-methyl-2,5-dimethoxy-amphetamine) can take 2 to 3 hours for the onset of effects, as compared to 1 to 2 hours for LSD (lysergic acid diethylamide). Both DOM and LSD are highly abuseable Schedule I substances, well known drugs of abuse, and widely abused, despite their difference in onset times. The drug abuser evidently is willing to wait for the effects of DOM to begin and may even enjoy the period of anticipation before onset of the drug's effects.

#### *Similarity to Gabapentin*

Pfizer maintains that pregabalin is similar to the nonscheduled gabapentin, and that gabapentin is not a drug of abuse. Therefore, the sponsor concludes that pregabalin will not be a drug of abuse. The view that the drugs are similar is based solely on the similar neurochemistry of the two drugs. From a medicinal chemistry viewpoint, the structural differences between the pregabalin and gabapentin molecules would not necessarily lead one to conclude that they possess identical pharmacological activity. Additionally, Pfizer acknowledged in an April 2004 meeting that no direct comparison of abuse liability of the two drugs from human laboratory studies exists.

Regarding the neurochemistry similarities, animal receptor binding studies conducted by Pfizer and submitted in the NDA show that pregabalin has high affinity binding for the alpha2-delta1 and alpha2-delta2 sites of the calcium channel. Sites screened but found to be negative included receptors, channels and transporters that are associated with known drugs of abuse. These include the GABA, dopamine, serotonin, acetylcholine, opioid, cannabinoid, and NMDA sites. The mechanism of action of pregabalin is not well understood, and the significance of the involvement of the alpha-delta sites of the calcium channel relative to abuse potential is unknown.

One cannot conclude at this time that because Pfizer considers gabapentin not to be a drug of abuse, that pregabalin is so-similar that it would not be abused. Although Pfizer considers gabapentin not to be a drug of abuse, the Drug Abuse Warning Network (DAWN) does provide a possible "abuse signal." CSS reviewed DAWN data and found that between 1997 and 2002, thousands of emergency department (ED) mentions related to abuse of gabapentin are listed. The circumstances and significance of these reports are not known at this time, but the DAWN reports which represent actual cases related to abuse need to be evaluated in considering Pfizer's argument on their relevance to the abuse potential assessment of pregabalin. Analysis needs to include motivation for use,

other drugs taken in combination with gabapentin, frequency of use, and dose administered.

Scheduling at the time of first marketing of a drug is based on the abuse potential of the drug, as determined from data from scientific studies. The CSA allows for a drug to be rescheduled at a later time as new data relative to the abuse potential and risk to the public health are obtained after a drug is marketed.

## **2. Euphoria In Clinical Trials (see Table 1, page 2)**

Euphoria is a subjective effect often sought by drug abusers. "Euphoria" refers to terms provided by the sponsor: "high", "stoned", "elation", "elevated mood", "intoxicated", "increased well-being", and "excessive happiness", as well as additional terms selected by CSS: "drugged, drunk, giddy, mood swings, hallucinations, floating, feeling addicted."

In the absence of a euphoria-related term, CSS selected a term that indicated a drug effect known to be associated with other drugs of abuse: "decreased concentration, disoriented, decreased memory, lightheaded, spacey, confusion, mental slowing, groggy, stupor, woozy, muzzy, mental disturbance, delirious, disconnected, derealization, dissociation, detached, depersonalization, psychomotor stimulation, jittery, edgy."

In addition, other terms included "intentional overdose," "overdose" and "suicide."

According to the Sponsor, there are a total of 423 patients, of the 8666 who received pregabalin in the controlled and uncontrolled trials, who experienced euphoria, for a total rate of 4.9%. Out of these 423 patients who had euphoria, 26 (6.1%) dropped out of the study following the reporting of this adverse event.

Further, according to the sponsor, of the 5508 patients who received pregabalin in controlled trials, there were 205 who had euphoria (3.7%). A break-down of the number of these patients who dropped out due to this adverse event was not provided.

As a comparison, the rate of euphoria for gabapentin is listed in the label as "infrequent," meaning an incidence of between 1/100 and 1/1000. The Drug Abuse and Dependence section states that, "The abuse and dependence potential of Neurontin<sup>®</sup> has not been evaluated in human studies."

CSS reviewed approximately 2,000 case report forms (CRFs) submitted in the NDA that included adverse events related to a demonstration of euphoria in the clinical trials. Although often times the subjects in the clinical trials reported more than one adverse event, for this review CSS focused on only those adverse events for each individual subject that were likely to be abuse-related, with the assessment of the euphoria-related

adverse event the primary goal. The selection was based on the term that best indicated a euphoric reaction, which included terms on the Sponsor's list as well as additional terms (drugged, drunk, giddy, mood swings, hallucinations, floating, feeling addicted). In the absence of a euphoria-related term, CSS selected a term that indicated a drug effect known to be associated with other drugs of abuse. These included decreased concentration, disoriented, decreased memory, lightheaded, spacey, confusion, mental slowing, groggy, stupor, woozy, muzzy, mental disturbance, delirious, disconnected, derealization, dissociation, detached, depersonalization, psychomotor stimulation, jittery, and edgy.

The results of the CSS analysis (in Table 1, page 2) show the following:

- \* In the seven clinical trials for Generalized Anxiety Disorder (GAD), there were 29 patients who had a "euphoric" adverse event. An additional 41 subjects had adverse events that indicated reactions known to be associated with drugs of abuse. Thus, a total of 70 individuals (out of 1149 patients who participated in GAD trials, 6.1 %) had CNS reactions associated with drugs of abuse. Thirty-seven of the 70 (53%) individuals who had an adverse event indicative of drug abuse had multiple incidents of the adverse events. Sixty of the 70 patients (86%) of these incidents were mild to moderate in severity, but 10 patients (14%) had severe reactions. Thirty-two of the 70 individuals (46%) were discontinued from the study following the reporting of the adverse event. Additionally, one GAD study (#1008-088) initiated with an 8-week open label pregabalin treatment followed by a 24-week randomized, double-blind, placebo-controlled treatment phase. Subjects who experienced euphoria during the open label phase were not included in the double-blind phase.
- \* The case reports often did not include the dose an individual received when more than one dose was tested in a study. However, in one GAD trial (1008-088) that only tested 450 mg of pregabalin, 19 of 168 patients (11.3%) had an adverse event associated with drugs of abuse.
- \* Review of the three epilepsy trials revealed reports from 12 patients who had a "euphoric" adverse event and an additional 37 patients who had an adverse event associated with drugs of abuse. Thus, 49 patients of 758 who participated in epilepsy trials (6.5%) had CNS reactions associated with drugs of abuse. The majority of patients (35 of 49 patients, 71%) had multiple incidents of these adverse events. Most (47 of the 49 patients, 96%) had adverse events that were mild to moderate in severity, while 2 (4%) had severe adverse events. Eighteen of the 49 subjects (37%) dropped out of the study due to the adverse event.
- \* Review of the case report forms in the 11 neuropathic pain trials identified 37 patients who had a "euphoric" adverse event as coded by the sponsor and an additional 88 patients who had an adverse event associated with drugs of abuse. Thus, 125 patients of 1,831

who participated in neuropathic pain trials (6.8%) had CNS reactions associated with drugs of abuse. Seventy-four of the 125 patients (59%) had multiple incidents of these adverse events. Of the 125 patients, 111 (89%) had adverse events that were mild to moderate in severity, while 21 (17%) had severe adverse events. Fifty-seven of the 125 subjects (46%) dropped out of the study due to the adverse event.

### *Data Limitations*

CSS reviewed and had access to approximately 2,000 CRFs for subjects receiving pregabalin from the efficacy trials. The sponsor was only required to submit those CRFs where there were adverse events. The complete pharmacokinetic CRFs were not available to CSS for review. The rate of euphoria in the 28 gabapentin clinical trials could not be determined as we did not have access to those data.

### **3. Human Abuse Liability Study**

Pfizer's initial strategy to assess the abuse liability in humans was to compare subjective and reinforcing effects of pregabalin to an active control, a drug which is marketed for a similar therapeutic indication and has known abuse liability.

Pregabalin was compared to diazepam. Diazepam is a prototypic CNS depressant drug of abuse. Diazepam is used extensively in human studies designed to assess abuse liability of other anxiolytic drugs. The sponsor selected diazepam as a positive control because it is a Schedule IV controlled substance with anxiolytic and sedative properties and pregabalin was expected to have anxiolytic and sedative effects. On measures of mood using subjects who use diazepam or other similar agents recreationally (including alcohol), diazepam produces increases in measures of euphoria and sedation and decreases in measures of alertness and arousal. In drug-taking studies, diazepam is preferred over placebo and is self-administered to intoxicating levels. Comparing the subjective and reinforcing effects of pregabalin to those of diazepam and placebo in a population of recreational sedative/alcohol subjects provide information in evaluating the abuse potential of pregabalin.

Subjects were eligible for the study if they drank more than 12 drinks of alcohol per week or previously used sedatives recreationally to get high at least 6 times. Subjects participated in one practice session and 5 drug sessions that included a minimum of a 5-day washout period between sessions. The effects of the study medication were evaluated using subjective scales including POMS, ARCI, and VAS completed 0.2 hours before drug, and 0.5, 1, 2, 3, 4, 5, and 6 hours post drug administration. At 6 hours post-drug administration, the End of Session Questionnaire (EOSQ) and Multiple Choice Form were completed. After a minimum 5-day washout period following study participation, subjects returned for a post-study visit for an examination. Subjects then participated in

the Multiple Choice Procedure (MCP) in which they received drug or money, and a final follow-up session where screening tests were repeated and subjects were debriefed.

The magnitude of the effects of 200 mg pregabalin was similar to those of 15 mg diazepam, but these effects peaked at least 1 hour later. Similarly, 15 mg diazepam was identified as a sedative by 53% of the subjects and 200 mg pregabalin was identified as a sedative by 73%. The profile of effects of the 450 mg pregabalin dose was mixed. While there were significant increases on several measures indicating sedative-like effects, these effects were less than those of the lower dose of pregabalin and sometimes failed to reach statistical significance relative to placebo. The 450 mg pregabalin dose was identified as a sedative by only 40% of the subjects and as a stimulant by 40% of the subjects. There were some trends on the subjective effects questionnaires suggesting that 450 mg had stimulant-like effects. On measures of "Good Drug Effects" and "High," the effects of 450 mg of pregabalin were similar in magnitude and direction to 30 mg diazepam.

The MCP, a human self-administration procedure, is used in assessing reinforcing effects. In the present study, the procedure did not differentiate between placebo and diazepam and is not a valid measure to address the issue of reinforcing effects of the test drug, pregabalin. Thus, the results of this part of the study do not contribute to the overall assessment of abuse liability.

Pfizer and its investigators reached the following conclusions regarding the study:

1. The profile of subjective effects of diazepam in recreational sedative/alcohol using subjects was consistent with prior findings for diazepam and related anxiolytics. Diazepam served as an acceptable positive control for evaluating the subjective effects of pregabalin.
2. The 200 mg dose of pregabalin produced statistically significant effects compared to placebo on several subjective effects measures. Arousal (POMS) was decreased, whereas Confusion (POMS), Fatigue (POMS), Good Drug Effect (VAS), High (VAS), Sedated (VAS), and Tired (VAS) were increased. The profile was similar to the profile for the 15 mg dose of diazepam by most of the subjects who identified it as a sedative.
3. The 450 mg dose of pregabalin produced statistically significant effects compared to placebo on several subjective effects measures. Sedated (VAS), Confusion (POMS), Good Drug Effect (VAS), and High (VAS) increased. This dose differed from 30 mg diazepam on many scales, indicating more stimulant-like effects. Relative to diazepam, 450 mg pregabalin increased Arousal (POMS), BG (ARCI), and Alert (VAS). The profile of 450 mg pregabalin was similar to 30 mg diazepam in some respects (such as Good Drug Effect) but there were substantial differences on many measures of sedation. Unlike 30 mg diazepam, pregabalin 450 mg was not consistently identified as a sedative. Thus, there were similarities and differences between 450 mg pregabalin and 30 mg diazepam.

4. MCP showed no difference between diazepam and placebo. Thus, the MCP failed in its ability to evaluate any potentially reinforcing value of pregabalin.

*Sponsor's Statistical Analysis of Study*

The sponsor selected far too many primary endpoints: crossover point on the MCP, and comparisons between treatment groups on a number of subjective measures, specifically: POMS (10 subscales), VAS (19 scales), ARCI (5 subscales) scores, and the End of Session Questionnaire (EOSQ).

Table 2. Parameters with a Statistically Significant Difference ( $p < 0.05$ ) Between Drug and Placebo (Source: NDA 21-446)

Parameter <sup>a</sup>	Pregabalin 200 mg	Pregabalin 450 mg	Diazepam 15 mg	Diazepam 30 mg
POMS Arousal	↓	↑	NS	↓
POMS Confusion	↑	↑	↑	↑
POMS Fatigue	↑	NS	NS	↑
ARCI Sedation: PCAG	NS	NS	NS	↑
VAS Alert	NS	NS	NS	↓
VAS Good Drug Effect	↑	↑	↑	↑
VAS High	↑	↑	↑	↑
VAS Sedated	↑	↑	↑	↑
VAS Tired	↑	NS	↑	↑

NS = Not significant; POMS = Profile of Moods States; ARCI = Addiction Research Center Inventory; VAS = Visual Analogue Scale; PCAG = Pentobarbital-Chlorpromazine-Alcohol Group.

<sup>a</sup> Parameters with a statistically significant ( $p < 0.05$ ) drug main effect or drug-by-time interaction. In the case where drug main effect or drug-by-time interaction was significant, ↑ indicates drug had significantly higher values than placebo for at least one time point on individual time-point comparisons; ↓ indicates drug had significantly lower values than placebo for at least one time point on individual time-point comparisons.

In comparison between placebo and each drug group, measures that had a statistically significant difference between study drug and placebo according to the sponsor's analysis are reproduced in Table 2 (above). The arrows indicate whether the drug had higher (↑) or lower (↓) values for a given parameter, relative to placebo. In addition to MCP, the following measures did not differ statistically significantly between placebo and any of the study drugs in their analysis: ARCI (Amphetamine Group, MBG, LSD); POMS

(Vigor, Friendliness, Elation, Positive Mood, Anger, Depression, Anxiety); VAS (Drug Liking, Stimulated, Friendly, Talkative, Self-confident, Social, Bad Drug Effect, Miserable, Irritable, Anxious, Down, Hungry, On Edge, Confused); EOSQ (Drug Liking). The ARCI Dysphoria scale, VAS Drug Liking, VAS Stimulated, and EOSQ Drug Liking were all associated with p-values of 0.05-0.10 for main drug effect.

Table 3. Parameters with a Statistically Significant Difference ( $p < 0.05$ ) Between Pregabalin and Diazepam (Source: NDA 21-446)

Parameter <sup>a</sup>	Diazepam 15 mg versus		Diazepam 30 mg versus	
	Pregabalin 200 mg	Pregabalin 450 mg	Pregabalin 200 mg	Pregabalin 450 mg
POMS Arousal	↓	↑	↑	↑
POMS Confusion	↓↑	↓↑	↓	↓↑
POMS Fatigue	↑	↓↑	↓	↓
ARCI Stimulant-Like Effects: BG	NS	NS	NS	↑
ARCI Sedation: PCAG	↑	↓	↓	↓
VAS Alert	NS	↑	NS	↑
VAS Good Drug Effect	NS	↓↑	↓	↓
VAS High	NS	↓↑	↓	↓↑
VAS Sedated	NS	↓↑	↓	↓
VAS Tired	↑	NS	↓	↓

NS = Not significant; POMS = Profile of Moods States; ARCI = Addiction Research Center Inventory; VAS = Visual Analogue Scale; BG = Benzedrine Group; PCAG = Pentobarbital-Chlorpromazine-Alcohol Group.

<sup>a</sup> Parameters with a statistically significant ( $p < 0.05$ ) drug main effect or drug-by-time interaction. In the case where drug main effect or drug-by-time interaction was significant, ↑ indicates pregabalin had significantly higher values than diazepam for at least one time point on individual time-point comparisons; ↓ indicates pregabalin had significantly lower values than diazepam for at least one time point on individual time-point comparisons.

<sup>b</sup> Direction of difference changed over time.

Table 3 (above) shows comparisons and statistically significant differences between pregabalin and diazepam. Subjective effects produced by pregabalin 200 mg and diazepam 15 mg were similar, in that both produced sedative effects (VAS-Sedated, VAS-Tired). The majority of subjects identified the low dose of both pregabalin and diazepam on the EOSQ as a sedative. Except for Sedated (VAS), there were no sedative-

like effects of the 450 mg dose of pregabalin versus placebo. The 450 mg dose of pregabalin differed from 30 mg diazepam on many scales indicating more stimulant-like effects. Relative to diazepam, 450 mg pregabalin increased Arousal (POMS), Benzedrine (BG; ARCI), and Alert (VAS). The profile of 450 mg pregabalin was similar to 30 mg diazepam in "Good Drug Effects", for example, though there were substantial differences on many measures of sedation. Unlike 30 mg diazepam, pregabalin 450 mg was not consistently identified as a sedative on the EOSQ, as described above.

### *FDA Statistical Analysis of Study*

#### *Primary Variables*

For all primary variables, pregabalin has larger mean response than placebo. Also, pregabalin has no statistically significant lower mean response than diazepam. The sponsor failed to show that pregabalin has no potential for abuse liability relative to diazepam which has recognized abuse liability and is controlled in CSA Schedule IV.

The primary parameters of potential abuse of pregabalin used in this study are as follows:

1. VAS: Emax of Liking
2. VAS: Emax of Good Drug Effect
3. VAS: Emax of High
4. End of Session Questionnaire: Emax of Drug Liking

In order to claim that pregabalin has no potential for abuse, for each primary variable the applicant must show that:

1. Diazepam has statistically larger mean response than placebo to insure the validation of the positive control of diazepam
2. Pregabalin has statistically lower mean response than double of the mean response of placebo
3. Pregabalin has statistically lower mean response than diazepam.

The treatment effects of the primary variables (Emax of Drug Liking, using the End of Session Questionnaire; VAS: Emax of Liking; VAS: Emax of Good Drug Effect; VAS: Emax of High) are statistically significant at 5% level, except for that of Good Drug Effect, which has a p-value of 0.1019. The given significance level of each test is 5%.

For all primary variables, there is insufficient evidence to indicate that pregabalin has statistically lower mean response than diazepam. In most cases, the observed mean response of pregabalin is greater than that of diazepam, and from those tests 75% of the p-values exceed 0.5 and 58% of them exceed 0.7. For all primary variables, there is insufficient evidence to indicate that pregabalin has a lower mean response than double

the mean response of placebo. The range of p-values for those tests is from 0.3092 to 0.9324. Also, there is strong evidence to indicate that mean response of pregabalin is greater than that of placebo for all primary variables. Since diazepam has a statistically significant difference in mean response from placebo at 5%, the study results are valid. Therefore, pregabalin appears to have the same liability for abuse as diazepam.

### *Secondary Variables*

Many of the secondary variables show similar or somewhat greater response from the 450 mg pregabalin dose relative to the 30 mg diazepam in most of the secondary variables.

Secondary variables considered in this analysis are as follows:

1. VAS: Emax of Stimulated
  2. VAS: Emax of Sedated
  3. ARCI: Emax of MBG
  4. ARCI: Emax of PCAG
  5. ARCI: Emax of LSD
  6. ARCI: Emax of BG
  7. End of Session: Drug Identification
- 
1. Diazepam (15 mg and 30 mg) versus placebo for the variable Stimulated (VAS) was not statistically valid. The statistical analysis for variable Sedated (VAS) is valid showing that both diazepam and pregabalin rated greater than placebo for their sedating effects. Also, the 450 mg dose of pregabalin produced a higher mean response than 30 mg diazepam for Stimulated (VAS).
  2. In the EOSQ, 40% of study subjects rated the high dose of pregabalin as a sedative and 40% rated it as a stimulant. Large placebo effects were observed for 15 mg diazepam (40%) and 450 mg pregabalin (20%).
  3. Subscales of the ARCI failed to demonstrate similar results. Diazepam (15 mg and 30 mg) versus placebo for the BG (ARCI) was not statistically valid. The MBG and LSD subscales of the ARCI showed statistically insignificant lower mean responses for pregabalin relative to diazepam. Analysis of the PCAG subscale showed that both doses of pregabalin have lower mean response than double placebo and 30 mg diazepam. This is explained by the lack of suitable application of the ARCI questions to recreational users of sedatives and alcohol, as demonstrated by the high placebo responses on all ARCI subscales. The ARCI is more suitable for individuals who are abusers of opiates and amphetamine-like stimulants which is not the case with the present study population. Unpredictable or inconsistent results can be expected from individuals who are primarily abusers of benzodiazepines or alcohol.

#### 4. Drug Abuse Warning Network (DAWN) Data on Gabapentin

Pfizer has maintained that gabapentin is not a drug of abuse or misuse and that because of its similarity to pregabalin one would predict that the latter would not be abused or misused. The sponsor submitted DAWN data showing that gabapentin had fewer total emergency department (ED) mentions than alprazolam (Schedule IV) and hydrocodone (Schedule II & III) for the years 1997-2002 (Table 4). Nevertheless, thousands of mentions of abuse of gabapentin are listed in DAWN.

Table 4. Number of Emergency Department Drug Mentions (1997-2002).

Year	Gabapentin	Alprazolam	Hydrocodone
1997	296	17,468	11,570
1998	1,002	17,833	13,611
1999	2,395	20,484	15,252
2000	4,465	22,105	20,098
2001	3,461	25,644	21,567
2002	4,465	27,659	25,197

In conclusion, based on the most recent DAWN data that are available, gabapentin has been reported responsible for hospital emergency department mentions associated with abuse or misuse. More in depth analysis of the ED episodes is needed in order to ascertain the circumstances of these events. In depth analysis of DAWN data needs to consider information related to motivation for drug use, dose of drug, other drugs taken in combination, and the duration of drug use.

Additionally, one must consider the relative availability of the drugs that are being compared. For example, in terms of frequency of prescribing, alprazolam (#11) and hydrocodone (#1) are greater than gabapentin (#36). Their relative prescribing rankings are in parenthesis ( ).

Finally, other sources of drug abuse data need to be investigated as well to determine the extent and significance of abuse of gabapentin.

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Corinne Moody  
9/1/04 12:22:01 PM  
CSO  
Corinne P. Moody for CSS

Michael Klein  
9/1/04 12:30:28 PM  
CHEMIST  
Signing for Deborah Leiderman, MD, Director, CSS

8/30/04

**NDA 21-446**

**LYRICA (pregabalin) Capsules, 25, 50, 75, 100 mg**

**CHEMISTRY DIVISION DIRECTOR REVIEW**

**Applicant:**

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, MI

**Indication:** Neuropathic Pain

**Presentation:** blisters 4 X 6 capsules/card, and 60 count HDPE bottles ( a 500 count bottle is approvable and will be introduced post approval)

**EER Status:** Acceptable 22\_JUN\_2004

**Consults:** DMETS – Tradename: LYRICA - acceptable 15-MAR-2004  
Statistics – none  
EA – no consult - waiver requested – granted

**Phase IV Commitments:** The first 3 lots of drug substance manufactured at the Ringaskiddy IRE facility using [ ] will be tested for [ ]

The original NDA was received 30-OCT-2003

**NDA 21-446 is the lead NDA for CMC review for [ ] [ ] for pregabalin:**

**NDA 21-723 for PHN in HFD-170 (added strengths 150, 200, 225, 300 mg)**  
[ ] [ ]

Note that an amendment submitted 30-AUG-2004 will not be reviewed in this review cycle.

The **drug substance** is manufactured by:

Pfizer Ireland, Inc.  
Ringaskiddy, IRE

Manufacturing and controls information was reviewed and were found acceptable. Of note was the issue of the potential carcinogenic impurity [ ] which could be formed during [ ] of the drug substance from [ ]

[ ] Data were provided from the analyses of [ ] batches for [ ] and none was detected. The level of quantitation was [ ] ppm. This is considered adequate. No controls for this potential impurity are considered needed. A [ ] process was proposed so a phase 4 commitment was made to test the first 3 lots of drug substance manufactured at the Ringaskiddy IRE facility using [ ]

[ ] Comparability protocols providing [ ] manufacturing processes were found acceptable following the establishment of added controls. The [ ] manufacturing protocols provide [ ]

[ ] Structural alerts for mutagenicity are present [ ] so added controls were required to be established. The added controls [ ]

[ ] of pregabalin [ ] highly effective.

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. A re-test period of [ ] was requested, and is supported by 36 months submitted stability data on only pilot scale batches from the R&D site - a [ ] re-test was granted. The stability testing protocol is considered adequate.

### Conclusion

Drug substance is satisfactory.

The **drug product** is capsules of 25, 50, 75, 100 mg.

Manufacturer:

Parke Davis, Div Warner Lambert Co.  
Vega Baja, PR

The manufacturing method is [ ] process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The submitted stability data is adequate to support the 36 month expiry in all presentations.

[ ] The stability testing protocol is considered adequate. The established name pregabalin is USAN.

Labeling is acceptable.

The overall Compliance recommendation is acceptable as of 22-JUN-2004.

All associated DMFs are acceptable

**Overall Conclusion**

From a CMC perspective the application is recommended for an approvable action.

Eric P Duffy, PhD  
Director, DNDC II/ONDC

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Eric Duffy  
8/30/04 05:44:46 PM  
CHEMIST

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** August 25, 2004  
**TO:** NDA 21-446 Study File  
**FROM:** Lisa Malandro  
**SUBJECT:** **Post-Action Meeting**  
NDA 21-446, LYRICA (pregabalin) Capsules

A post-action meeting was scheduled with the Sponsor for August 18, 2004 at 3:30 pm via telephone conversation prior to receipt of the official meeting request to ensure that the meeting would be held prior [ Due to the timing of the meeting, a letter confirming the meeting date and time was not generated.

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On Original*

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/s/

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Lisa Malandro  
8/25/04 11:29:36 AM

8/18/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-446

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS  
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to your October 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 20/50/75/100/150/200/225/300 mg.

We also refer to the post-action meeting between representatives of your firm and the FDA on August 18, 2004. The purpose of the meeting was to review the ophthalmologic data in an attempt for to reach agreement on interpretation of the ophthalmologic findings to allow for finalization of the label.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7416.

Sincerely,

*{See attached electronic signature page}*

**ps**  
Lisa Marie Malandro  
Regulatory Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** August 18, 2004  
**TIME:** 3:30 – 5:30 pm  
**LOCATION:** Parklawn Building, Potomac Conference Room  
**APPLICATION:** 21-446  
**DRUG NAME:** LYRICA (pregabalin) Capsules  
**TYPE OF MEETING:** Type B, Post-action meeting

**MEETING CHAIRS:** Bob Meyer, MD and Robert Temple, MD

**MEETING RECORDER:** Lisa Malandro

**FDA ATTENDEES:**

HFD-170

Bob Meyer, MD	Director, Office of New Drugs II
Bob A. Rappaport, MD	Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Mwango Kashoki, MD, MPH	Medical Officer
Lisa Malandro	Regulatory Project Manager

HFD-550

Wiley Chambers, MD	Deputy Division Director
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HFD-120

Robert Temple, MD	Director, Office of New Drugs I
John Feeney, MD	Neurology Team Leader
Alice Hughes, MD	Safety Team Reviewer

**EXTERNAL CONSTITUENT ATTENDEES:**

Toni Hoover, PhD	Development Leader
Paul Nitschmann, MD	Regulatory
Jonathon Parker	Regulatory
Kathleen Dowd	Team Leader
Richard Kavoussi, MD	Clinical
Kevin Chartier, PhD	Statistics
Mark Pierce, MD	Clinical
Mitch Brigell, PhD	Clinical
[ ]	Consultant
[ ]	Consultant

## **BACKGROUND:**

This meeting was a continuation of previous discussions regarding the ophthalmologic findings from clinical trials of pregabalin. Most recently, a teleconference (June 16, 2004) and a meeting (July 14, 2004) focused solely on these issues and resulted in the inability to come to agreement on the precautionary language in the label. Following receipt of an "approvable" action on July 26, 2004, Pfizer requested a post-action meeting to discuss the ophthalmologic data in more detail with appropriate representation from the Divisions and Offices involved in their four applications (NDA 21-446, 21-723, 21-724, and 21-725) in order to attempt to reach agreement on appropriate precautionary language in the label.

## **MEETING OBJECTIVES:**

The purpose of the meeting was to review the ophthalmologic data in an attempt to reach agreement on interpretation of the ophthalmologic findings to allow for finalization of the label.

## **DISCUSSION POINTS:**

The meeting began with a presentation of the history of Pfizer's conclusions regarding visual field and visual acuity testing. The slides that Pfizer presented are attached to these meeting minutes.

After review of the results from the controlled data, Pfizer discussed 10 cases that were of particular interest to them from the open-label experience. While no one case definition was applied to identify these 10 cases, it was clear from the discussion that at least some of the cases were identified because they experienced binasal field cuts, a pattern of field loss that has been linked in some reports to vigabatrin, a structurally similar drug.

While Pfizer maintained that the 10 cases of interest for the most part showed resolution of the field defects, Dr. Chambers believed the evidence for improvement was much less certain. In part, this was due to some inaccuracies in describing the evolution of the cases present in previous documents reviewed by Dr. Chambers. Nevertheless, Pfizer's representatives contended that similar cases probably existed in controlled trials for even the placebo-treated patients, and that the overall number of otherwise worrisome cases in the uncontrolled data was small. The cases from controlled experience lacked the longitudinal follow-up, however.

Pfizer's representatives stated that they had not identified a field loss in pregabalin-treated patients that exactly matched the field loss characteristic of vigabatrin. Pfizer acknowledged that the ten patients' fields were not all normal, but also stated that they were not definitively due to drug. Pfizer concluded that among the ten abnormal cases, there is no pattern or reason to believe a group of them had drug-related visual field defects.

Dr. Chambers stated that most of these cases did, in fact, become worse over time. Sometimes the pattern was different as it evolved, but clearly did not return to normal or sometimes even to baseline.

Dr. Chambers pointed out that overall the data collection was inadequate, that threshold testing should have been performed, and that follow-up was erratic. Some of the resolved visual field defects were collected after discontinuation of drug (in many cases 2.5 years following drug discontinuation) and we do not know what would have happened if drug had been continued.

In light of the results from controlled-trial experience, the attendees discussed briefly whether it was feasible and worthwhile to recommend monitoring for ophthalmologic changes. The "validated" data on visual fields was less impressive than the "all cases" analysis of visual fields. With respect to visual acuity, patients can tell if they are experiencing visual acuity changes, therefore, monitoring is not as necessary. Due to the variability of visual field testing, Pfizer expressed concern that slight variation in visual field tests would cause many pregabalin patients to stop taking a beneficial drug even though a similar percent of placebo patients would experience similar visual field defects. Pfizer is also concerned that the strong language proposed by the Agency would cause physicians and patients to compare the findings in pregabalin to those in vigabatrin.

During the discussion of the controlled data, it became clear that one of the epilepsy trials included in the pooled controlled trial data on visual fields incorporated only crude confrontational visual field testing and therefore should not be factored into the occurrence rate of visual field disturbances, as it adds no information to the numerator. There was general agreement that this data should not be pooled with the other visual field testing.

#### **ACTION ITEM:**

Drs. Meyer, Temple, and Chambers agreed to discuss and reconsider this information and to provide Pfizer with a recommendation for the precautionary language in the label.

#### **FDA RECOMMENDATION FOLLOWING THE MEETING:**

Drs. Meyer and Temple recommended that the most recent proposed precautionary wording from Pfizer was acceptable with two modifications:

1. The relative percent that was previously calculated based upon the number of validated cases should be re-calculated based upon the total number of cases.
2. The re-calculation of the relative percent also should not include the epilepsy study in which only confrontational visual field testing was performed.

This recommendation was communicated to Pfizer via telephone on Friday, August 20, 2004.

**ATTACHMENT:**

1. Slides presented by Pfizer at the meeting.

18 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

### Office Director's Sign-Off Memorandum

Date: Wednesday, July 28, 2004  
NDA: 21-446  
Sponsor: Pfizer  
Proprietary Name: LYRICA (Pregabalin) Capsules  
From: Robert J. Meyer, MD  
Director, ODE II

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**Introduction:** The review for LYRICA (pregabalin), a new molecular entity, is on its first cycle. LYRICA is a single enantiomer (S) that is reported to be a gamma-aminobutyric acid (GABA) analogue that is under development for a number of neurologic and psychiatric indications. This NDA is for the treatment of pain in the setting of diabetic peripheral neuropathy. This is an area of unmet medical need, with little in the way of proven therapy and no FDA-approved drugs carry this indication. This was the basis for the priority designation.

The molecule is reportedly an alpha-2-delta ligand at CNS calcium channels, acting on the excitatory, GABA-related pathways in the CNS in a way similar to gabapentin. It does not have intrinsic activity at the GABA receptors themselves, however, nor at benzodiazepine receptors and is not reported to affect GABA degradation or re-uptake. This drug is the basis for applications submitted to FDA for the treatment of diabetic neuropathic pain (this NDA), post-herpetic neuralgia, generalized anxiety disorder, and as an adjunct treatment of epilepsy. These applications were administratively split into multiple NDAs due to differing review divisions being involved and due to differing time lines. The drug was originally under development by Warner-Lambert and is submitted by Pfizer now that the former has been acquired by the latter.

Please see the primary, secondary and tertiary memos for this application. Dr. Rappaport's Division Director memo is excellent and I am in essential agreement with that memo. As is Dr. Rappaport, I am recommending approval of the drug for the treatment of pain in diabetic peripheral neuropathy. There are a number of phase 4 commitments that will be recommended in light of some of the unresolved issues arising from the review, none of which are of sufficient import to preclude approval at this point. These phase 4 commitments are enumerated at the end of this memorandum. There may be issues related to labeling and scheduling that may preclude an approval action at this time however. These issues are also expanded upon later in the memo.

**CMC:** LYRICA capsules are available in multiple dosage strengths: 25, 50, 75 and 100 mg capsules. There are no significant CMC issues remaining with pregabalin and the ONDC recommendation is for an approval.

Final recommendations from Compliance on the EERs is that the various sites involved in the production and testing of this product are acceptable as of June 22<sup>nd</sup>, 2004.

**Pharm/Tox:** This drug was extensively and appropriately studied preclinically and there are notable findings. The review was split between HFD-120 and 170 and I refer the reader to the appropriate primary and secondary reviews.

The target organs of toxicity in the chronic toxicity studies were bone marrow/hematology, the vascular system (tumors – see below), the skin, the kidneys and the reproductive system. Of note, there were dermatopathy findings in rats and monkeys, primarily on the tails. At higher doses, these lesions included frank necrosis and fibrosis. Interestingly, while these lesions often developed early in treatment, they also sometimes spontaneously resolved on continued dosing. Mechanistic studies did not clearly identify a causal mechanism. The primary PT review team views these findings as of significant concern, given the common problem in this diabetic neuropathic population of skin breakdown and ulceration.

Genotoxicity assays, in vitro and in vivo, were negative. The original mouse carcinogenicity study (done in the B6C3F1 strain) showed a dose-related occurrence of hemangiosarcomas. These tumors occurred in multiple anatomic sites, including the liver, spleen and bone marrow. There was a clear, statistical association at the 1000 and 5000 mg/kg doses, though there was a trend towards increased tumors compared to control even at the lower dose of 200 mg/kg, which resulted in serum AUCs similar to those at the therapeutic dose in humans. To explore whether this finding might be strain related, the sponsor undertook a second mouse carcinogenicity study with the CD-1 strain. While the tumors were somewhat less clearly associated with drug than in the prior study (particularly in female mice, where there was a high level of control tumors), there was again a finding of statistical association between the drug and the occurrence in hemangiosarcomas. The sponsor provided mechanistic studies having to do with platelet aggregation, and endothelial and megakaryocyte proliferation that appears to occur in these mouse strains, but not in human. While plausible, these studies were less than definitive and do not allow a conclusion that the findings are definitely not relevant to humans. However, it should also be noted that the rat carcinogenicity study was negative (and rats neither display the purported mechanistic findings).

The reproductive toxicology studies were remarkable, with multiple fetal effects particularly at the higher doses and the drug will be recommended to be a category C. The segment I studies showed some effects on fertility, specifically in rats there were decreased sperm counts, mobility and morphology. The NOAEL for these findings were 3 times the maximum recommended human dose, by exposure multiples. There was also delays in estrous cycles and fertility in female rats, with no NOAEL identified. Segment II studies showed some fetal abnormalities, largely of ossification.

**Biopharmaceutics:** Pregabalin was proposed by the sponsor to be used at either  $\mathcal{L}$   $\mathcal{L}$  per day, in divided doses ( $\mathcal{L}$   $\mathcal{L}$  three times daily). Due to tolerability issues, it is started at lower doses (e.g., 50 mg three times daily) and the dose advanced within a week if patients are properly tolerating the medication and appear to not have adequate pain control at this lower daily dose. Pregabalin is well absorbed (more than 90% orally bioavailable), with a relatively low volume of distribution (0.5

L/kg), and no appreciable binding to serum proteins. The terminal half-life is about 6 hours. The C<sub>max</sub> at steady state is approximately 5 mcg/ml at the 300 mg q 8 hour dosing regimen, with a T<sub>max</sub> of approximately 1.5 hours. There was a marginal food effect found, with food not greatly changing bioavailability, but leading to a 25 - 30% reduction in C<sub>max</sub> and a delayed T<sub>max</sub> out to 3 hours. The drug is not appreciably metabolized with approximately 98% of recovered radiolabeled drug recovered in the urine as unchanged parent. The most notable metabolite (accounting for just under 1% of the total drug) was the N-methylated derivative. There is no evidence of conversion of the S-enantiomer to the R-enantiomer in vivo. The drug displays linear PK over the relevant dose range and regimen. C<sub>ss</sub> is approximately 3 ug/ml at the daily dose of 300 mg. Though reasonably studied, it does not appear that pregabalin is associated with significant drug-drug interactions. Considering the low level of metabolism and the fact that the drug does not appreciably bind to plasma proteins, this is not unexpected. Of note, gabapentin co-administration did not lower the total exposure to pregabalin, but did lower the C<sub>max</sub>, similar to what was documented with food. The biopharmaceutics review team has not identified any issues to preclude approval.

**Clinical / Stastical**: The relevant portion of the clinical development program for this drug was focused on patients with established diabetic peripheral neuropathy and associated peripherally located pain. This population generally has long standing DM and the development of neuropathy frequently occurs in the setting of other DM complications, such as ophthalmologic, vascular, dermal, and renal complications. Therefore, they are both a vulnerable population, but also one in which there is a fair amount of potential confounding factors in the safety evaluation.

**Efficacy**: The sponsor performed five efficacy trials in the DM peripheral neuropathic pain population, four of which are regarded by the medical reviewers as adequate and well-controlled. The sponsor commendably explored a range of doses and dose regimens in these phase 3 studies. One of these trials examined twice daily dosing and, unfortunately, despite what might have been predicted from pharmacokinetics, this study failed to demonstrate efficacy. Therefore, the support of efficacy came from the remaining three adequate and well-controlled studies and supported only the three times daily dosing. One of these tested the 200 mg TID dosing (study 014, that also included a 50 mg TID dosing), one tested the 100 mg TID dose (study 131) and the last studied both the 100 mg and 200 mg TID dosing (study 029, that also included a 25 mg TID dose). Each of these studies was very similar in design, though of differing durations. Study 014 and study 131 were eight weeks in duration and study 029 had a 5 week treatment period. Otherwise, they were placebo-controlled, double blind, each enrolling approximately 70 to 90 patients per treatment group. The patients were diabetics with adequately (though not optimally) controlled diabetes with a diagnosis of distal, symmetric neuropathy and sufficiently symptomatic of pain to warrant treatment. Patients with significant concomitant diseases (hepatic, respiratory, cardiovascular disease, peripheral vascular disease, or hematologic illness) were excluded from these studies. Notably, patients with creatinine clearances under 60 mL/min were excluded from the trials, as were patients with overt CHF. Analgesics (other than acetaminophen or aspirin excepted) and other potential modulators of neuropathic pain (such as

antidepressants) were excluded during the trial. The primary endpoint for these trials was the weekly mean pain score, computed over the last 7 daily pain scores in the patient diary. Each of these studies showed a reduction of pain score greater with pregabalin compared to that seen with placebo (generally, approximating a point on this 11 point numeric scale) with secondary analyses (sleep interference, and other pain or general PROs) often also showed supportive evidence of efficacy. Notably, the 600 mg total daily dose showed no distinct marginal advantage over the 300 mg dose, while study 14 also provided evidence of efficacy of the 150 mg total daily dose, though this lower dose did appear marginally less effective than either 300 or 600 mg by direct or cross-study comparisons. Therefore, labeling allowing for use of 150 to 300 mg a day appears appropriate (not approving the 600 mg because it would allow for increased drug-related toxicities, but not apparently increased efficacy).

**Safety:** Because of the wide variety of indications studied, the safety database is very large for pregabalin, with over 8500 patients exposed to pregabalin in phase 2 and 3 studies, with over 1400 patients in the DPN program, with 201 exposed to pregabalin for 1 year or more. Please see the MO reviews and summary memos from Drs. Winchell and Rappaport for detailed discussions of safety. I will touch only on the notable positives and negatives.

While there were 68 deaths in the entire safety database for this compound through the 120-day update, and 17 in the DPN program, there was no evidence of either causality or an important imbalance compared to exposures suggesting a problem with pregabalin. There were more withdrawals for AEs in the treated group compared to placebo (9% vs. 4%) with the most frequent AEs leading to withdrawal of patients in the DPN program being dizziness, somnolence and headache. Less frequent were conditions such as blurred vision, confusion, peripheral edema, accidental injury, ataxia, uncoordination and abnormal thinking that led to more withdrawals with active than placebo. As for serious AEs, these were mostly balanced between active and placebo. Of note, however, is that accidental injuries appeared to occur more commonly in pregabalin and were the most frequent serious AEs. While this may be spurious, it may relate to sedation and/or incoordination reported by patients. It is also notable that, while slight, there were excess CV serious AEs with active vs. placebo, including CHF. This is important since this drug causes edema and weight gain.

There did not appear to be a signal of perturbations of glycemic control with the drug.

There were more eye events with active vs. placebo that the sponsor at least in part ascribes to the sedation/coordination issues of the drug. Dr. Chambers of HFD-550 has been kind enough to consult on the application and finds that there does appear to be a small, but important signal of visual disturbances with this drug – notably visual field loss and impaired acuity. These appear to be dose related. Dr. Chambers felt most of the changes to be minor and not likely to impair patient function, but did recommend good phase 4 studies to better define ophthalmologic effects of the drug with careful, rigorous testing of the visual fields, acuity and other aspects of visual quality and ocular integrity.

There was a clear signal of edema and weight gain with this drug, the latter of which could only partly be ascribed to clinically evident edema. Of note, an analysis of the

interrelationship between edema, weight gain and CHF in patients treated with/without pregabalin and patients with or without concomitant PPARs suggests at least an additive effect of the two drugs on edema and perhaps CHF. Given the recent concerns over PPARs, this potential PD interaction will need to be described in the precautions in the labeling.

Despite the preclinical concerns over skin lesions, there was no evidence of a dermal integrity problem with this drug, particularly when Dr. Permutt of the Biostatistics office did an analysis accounting for duration of exposure.

CSS did an analysis on abuse potential and are they are recommending scheduling. This is based, in part, on their opinion of self-administration in monkeys (albeit waning over time) and "likability" in addicts similar to or exceeding a benzodiazepine. There was also euphoria frequently reported in patients in the general anxiety disorder program relative to placebo. However, this latter finding was not evident in the DPN population.

#### **Labeling and nomenclature:**

DMETs has found the name for pregabalin – LYRICA - to be acceptable. We are having on-going discussions with the sponsor over a number of labeling issues, including ophthalmologic adverse effects and the propensity for abuse (and labeling for the proposed C-IV scheduling). We may well take an approvable action at this time due to an inability to satisfactorily come to resolution with the sponsor on all these issues prior to the PDUFA goal date.

#### **Regulatory Conclusions:**

LYRICA should be approved for use in the treatment of pain associated with diabetic peripheral neuropathy, once labeling and scheduling has been settled within the FDA and HHS. At the current time, the recommendation of CSS is for scheduling as a C-IV due to their findings of abuse potential. The following phase 4 commitments are to be made by Pfizer:

1. Complete an adequate and well-controlled clinical study or studies to better assess the ophthalmologic toxicity of pregabalin.
2. Complete an in-vitro study of pregabalin's propensity to induce CYP-enzyme metabolism.
3. Complete adequate and well-controlled clinical studies to assess the effect of pregabalin on nerve conduction velocity (NCV).

This latter study is in keeping with the current recommendations of the agency to assure us that an effective treatment of neuropathic pain does not produce its effect by further damaging neuronal pathways. The division had previously agreed to allow this as a phase 4 since Pfizer was not given this advice early enough to have this study be a part of this NDA. However, they have already started the study and depending on the resubmission timing, it is possible the results may be available prior to any approval.

Robert J. Meyer, MD  
Director,  
Office of Drug Evaluation II

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/s/

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Robert Meyer  
7/28/04 12:08:28 PM  
MEDICAL OFFICER

7/29/04

**ADRA Review #1 of Action Package for NDA 21-446, Lyrica (pregabalin) Capsules**

Reviewer: Lee Ripper, HFD-102

Date received: 6/4/04

Reviewed 6/8/04 and 7/28/04

Date original NDA received: 10/31/03

UF GOAL DATE: 7/31/04

ACTION GOAL DATE: ~~6/25/04~~ 7/29/04

Indication: Pain associated with diabetic peripheral neuropathy

Action type: *AE pending CSA scheduling and agreement on ophthalmologic warning in the labeling.*

RPM: Lisa Malandro

Drug Classification: 1P  
505(b)(1) application

Hard copy of forms: RPM confirmed that a signed, paper copy of the administrative forms was received.

Patent Info: Forms 3542a submitted for compound/pharmaceutical composition and 3 indications (seizure disorders, pain, anxiety)

Debarment Certification: AC

Safety Update: 2/23/04 MOR #1 page 223

Clinical Inspection Summary: 5 sites, data AC 6/7/04

ODS/DMETS Review of Trade Name: AC 5/18/04

DSRCS Review of PPI/MedGuide: 6/3/04

DDMAC Review: No review, PM confirmed that DDMAC attended labeling mtgs

EA: Rev #1 AC 2/25/04; FONSI 2/25/04

EER: AC 6/22/04

Financial Disclosure: AC

CMC section to Eric Duffy, 6/9/04

P/T section to Ken Hastings, 6/9/04. *Review into DFS 6/24/04.*

1. Need to add Exclusivity Summary to action package after it is put into DFS. *Not needed for AE action.*
2. Draft letter pending final decision on action (AE or AP).
3. Applicant has not submitted a draft MedGuide. See version drafted by DSRCS. Division is editing DSRCS version. *7/28/04: MedGuide downgraded to PPI.*
4. Latest division version of PI sent to Pfizer on 6/4. Company expects to respond on 6/14.
5. Need postmarketing commitments submission. *Not necessary at this time since action will be AE.*

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Lee Ripper  
ADRA, ODE II  
June 8 and July 28, 2004

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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 14, 2004  
**TIME:** 1:30 pm  
**LOCATION:** Parklawn Building, Conference Room C  
**APPLICATIONS:** 21-446, 21-723, 21-724, L **J**  
**DRUG NAME:** LYRICA (pregabalin) Capsules  
**TYPE OF MEETING:** TYPE C

**MEETING CHAIR:** Wiley Chambers, MD

**MEETING RECORDER:** Lisa Malandro

### **FDA ATTENDEES:** (Title and Office/Division)

Wiley Chambers, MD	Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP)
William Boyd, MD	DAAODP
Celia Winchell, MD	Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP)
Mwango Kashoki, MD, MPH	DACCADP
Lisa Malandro	DACCADP

### **EXTERNAL CONSTITUENT ATTENDEES:**

Jonathon Parker, RPh, MS	Regulatory
Betsy Garofalo, MD	Regulatory
Mitch Brigell, MD	Clinical
Rich Kavoussi, MD	Clinical

### **BACKGROUND:**

This meeting was a continuation of previous discussions regarding the ophthalmologic findings from clinical trials of pregabalin. Most recently, a teleconference held on June 16, 2004, focused solely on these issues. No consensus regarding the labeling language was reached at the teleconference. Following additional revisions by the Sponsor, this face-to-face meeting was scheduled so that the ophthalmologic data could be discussed in more detail in order to attempt to reach agreement on appropriate precautionary language in the label.

### **MEETING OBJECTIVES:**

The objective of this meeting was to discuss the ophthalmologic findings with regard to the labeling recommendations provided by the Agency to the Sponsor.

### **DISCUSSION POINTS:**

Discussion focused on three ophthalmologic findings: blurred vision, visual field defects and loss of visual acuity.

**Blurred Vision and Visual Acuity Changes:**

The Sponsor agrees with the Division that there is a dose-related increase in incidence of both blurred vision and visual acuity changes. The Sponsor believes that blurred vision is a "CNS effect" that occurs early in treatment, and is related to dizziness and somnolence, other "CNS effects" of pregabalin. The Sponsor feels that this change is the same as any change caused by a sedating CNS drug. Consequently, The Sponsor suggested that blurred vision should be included in the label as an adverse event that patients reported, but not as an ophthalmologic effect of pregabalin, *per se*.

With respect to pregabalin's effect on visual acuity, the Sponsor stated that the changes noted in the randomized clinical trials were mostly mild, monocular changes with no progression or trend. In support of this description of the nature of the visual acuity changes, the Sponsor cited follow-up data from patients in the randomized trials who met the definition of a visual acuity "case" in which no significant change in acuity was observed. Based on the data, the Sponsor agreed that a description of the visual acuity changes should be included in the label.

Dr. Chambers responded that the test for visual acuity, the Snellen test, was inadequate to fully exclude that the blurred vision was not related to an effect on the optic nerve. Dr. Chambers also disagreed that concurrent dizziness and somnolence were sufficient to explain the reports of blurred vision. Dr. Chambers stated that overall, the ophthalmologic testing that was performed was inadequate to rule out an effect of pregabalin on vision. He explained that the Sponsor essentially conducted a "basic screening" of patients' vision. More appropriate evaluations should have included best corrected visual acuity testing and threshold testing for visual fields with repeat testing for patients who were dizzy or somnolent. Also, there were errors in data collection. However, despite the inadequacy of the ophthalmologic evaluations, adverse findings were noted and need to be investigated further.

**Visual Field:**

The Sponsor stated that data from the controlled trials did not show a dose-related change in visual fields, based on "validated cases," meaning cases which were detected in screening and then independently reviewed by ophthalmologists. In a comparison of validated cases of visual field defects (pregabalin vs. placebo), the Sponsor found that only the odds ratio of pregabalin 300 mg/d vs. placebo reached statistical significance. When a similar comparison was conducted using data from just the population of patients with pain due to diabetic peripheral neuropathy (DPN), there was no evidence that treatment with pregabalin was associated with a higher risk of visual field defects, including the 300 mg/d dose. The Sponsor is of the opinion that the lack of a dose effect or a pattern of visual field changes across treatment groups means that the increased risk noted for the 300 mg/d group is a chance finding, without any clinical significance. The Sponsor also expressed that the methods used were intentionally designed to "cast a wide net," and to pick up all cases, even those of questionable significance, and that the validation procedure was intended to identify cases which were truly of concern. The majority of cases seen, it

was noted, involved scattered loss of a few points at the periphery, which is distinctly different from the visual field loss seen in association with vigabatrin. The Sponsor expressed concern that including a labeling statement about visual field loss would confuse practitioners, who would falsely associate pregabalin with the types of visual field changes seen in patients treated with vigabatrin.

Dr Chambers responded that the numbers of patients in the controlled trials were too small to expect a statistically significant difference in individual groups; lack of significance is not a demonstration that the effect is ignorable. In fact, because of the small sample size and insensitive nature of the testing, the presence of any statistically significant differences at all is surprising and cause for concern. Dr. Chambers also stated that he noted an increase in the frequency of visual field defects for patients in all trials who were treated with 300 mg/d. This finding is a 'signal' indicating the need for further investigation, as is the high rate of visual field abnormalities noted from the screening evaluation that was conducted. Dr. Chambers noted that he had examined the cases and disagreed with the Sponsor regarding which were "explained" noting that he did not agree that the visual field defects had alternate explanations other than an effect of pregabalin.

The Sponsor pointed out the high rate of visual field defects in the placebo group, which Dr. Chambers suggested could be reflective of "noise" due to poor testing methods. The Sponsor argued that, given the high occurrence of visual field defects in both the placebo and pregabalin groups, it cannot be concluded that the data show a true effect of pregabalin on visual fields. Consequently, the current wording recommended by the Agency is problematic since the incidence of visual field defects is so high placebo patients.

The Sponsor also pointed out that the open-label treatment data do not show an increase in the occurrence of visual field changes over time, as might be expected with long-term exposure. The Sponsor believes that this supports the conclusion that the increased frequency of defects noted for the 300 mg/d group is a chance finding. Dr. Chambers reiterated his opinion that the increased frequency of events for that dose group is sufficient to suggest that there is a drug effect that needs to be included in the product label and followed up on in post-marketing studies. Dr. Chambers stated that threshold testing of visual fields, with follow-up that includes adequate testing methods, would be appropriate for further evaluation. Until such testing is completed and reviewed by the Agency, the current precaution in the label recommending visual field monitoring for all patients is appropriate. The Sponsor inquired whether Dr. Chambers would review additional statistical approaches to the data. Dr. Chambers expressed willingness to review additional materials, but also indicated doubt that the currently-available data would support any other interpretation than a need for further testing, with precautionary labeling in place until data support its removal.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

The precautionary language, regarding ophthalmologic effects of pregabalin, as proposed by the Agency, was not agreed upon at this meeting. The Sponsor was invited to submit alternative language that might assuage their concern regarding confusion with vigabatrin, but encouraged to retain the statements included in the most recent language proposed by the Agency.

**ACTION ITEMS:**

The Sponsor will provide the Division with revised language for an ophthalmologic precaution in the package insert.

**ATTACHMENTS/HANDOUTS:**

- Attachment 1: Handout provided by the Sponsor at the meeting.
- Attachment 2: Handout provided by Dr. Chambers following the meeting.
- Attachment 3: Revisions to the Precautions section submitted by the Sponsor on July 20, 2004

ATTACHMENT 1

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

ATTACHMENT 2

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## List of Questions for Requested Meeting to Discuss the Visual Field Data

1) Given the preponderance of evidence across indications and with doses higher and lower than 300 mg/day showing no signal of an adverse effect on visual fields with pregabalin, what causes the Division to conclude that the results with the 300 mg/day dose are anything other than a by chance finding due to multiplicity among numerous statistical analyses?

### Response:

- The preponderance of evidence is that visual field defects were observed in the pregabalin clinical studies at a relatively high rate. The Summary of Visual Field Abnormalities from the MITT Population of Combined Controlled and Uncontrolled Studies reports a rate of 16.8% (582/3458). For a screening visual field test with a positive finding in every six people, it would seem prudent to recommend ophthalmological follow-up.*
- In controlled studies, the number of patients studied in each separate disease is too small to achieve sufficient power to detect statistically significant differences based on a screening test. Additionally, the doses studied for each indication are not exactly the same (300 mg was not studied in the anxiety indication.)*

	Placebo	P<300	300	450	600	Lorazepam	Placebo	P<300	300	450	600	Lorazepam	Placebo compar	300	600
Clinical	1062	772	523	197	769	109									
Ten or more miss	45	35	24	4	39	3	4%	5%	5%	2%	5%	3%			
Any VF	98	61	72	17	68	7	9%	8%	14%	9%	9%	6%			
	124	85	86	18	92	8	12%	11%	16%	9%	12%	7%			
Diabetic Neuropathy	237	141	144		148										
7-8wk	14	7	5		10		6%	5%	3%		7%		2%	-1%	
	24	12	14		18		10%	9%	10%		12%		0%	-2%	
	31	18	17		24		13%	13%	12%		16%		1%	-3%	
Postherpetic Neuropathy	163	153	25		56										
7-8wk	7	11	2		2		4%	7%	8%		4%		-4%	1%	
	24	16	6		8		15%	10%	24%		14%		-9%	0%	
	26	23	6		9		16%	15%	24%		16%		-8%	0%	
Chronic Pain	364	188	288	197	222										
8-12wk	12	2	10	4	13		3%	1%	3%	2%	6%		0%	-3%	
	30	15	47	17	25		8%	8%	16%	9%	11%		-8%	-3%	
	39	16	53	18	32		11%	9%	18%	9%	14%		-8%	-4%	
Epilepsy	141	122	66		191										
12wk	8	8	7		8		6%	7%	11%		4%		-5%	1%	
	7	12	5		9		5%	10%	8%		5%		-3%	0%	
	14	16	10		16		10%	13%	15%		8%		-5%	2%	
Anxiety	157	168			152	109									
5-12wk	4	7			6	3	3%	4%			4%	3%		-1%	
	13	6			8	7	8%	4%			5%	6%		3%	
	14	12			11	8	9%	7%			7%	7%		2%	

*As seen in the table above, the percentage of patients with visual field findings was higher in the 300mg dose than in the placebo group for all indications where a comparison was made except*

*diabetic neuropathy. For the Diabetic Neuropathy group, the percentage difference was 1% and the 600mg dose had higher rates than placebo*

2) If the Division maintains that the 300 mg/day dose finding is of concern, then:

a) What is the specific pattern of visual field change with pregabalin that differs from placebo and is of concern?

**Response:** *The pattern of visual field changes identified with pregabalin are scattered decreases predominately in the periphery. They could generally be detected by decreases in peripheral sensitivity.*

b) Could the Division please provide a list of patient numbers that show this pattern?

**Response:** *Patients of concern include the patients with visual fields identified by your VF experts and all of those who missed 10 or more points on the VF test. There is not agreement of the patients reported as resolved or explained.*

*Patient 014\_002013 is listed as having glaucoma as an explanation for the field loss, however, the cup to disc ratio is increased only in the left eye, not the right. The cup to disc ratio listed as abnormal is only 0.5 and the IOP is normal.*

*Patient 030\_118008 is listed as having new data with a normal right eye visual field. The visual field presented is not normal and the left eye is definitely worse.*

*Patient 034\_045003 is listed as having a normal follow-up exam. The VF performed at the follow-up was a 30 degree field, not a full field and did not evaluate where the defects were noted earlier.*

*Patient 105\_501002 is listed as showing a return to baseline OS and worse performance in the right eye with a comment of "poor concentration." Based on the times listed on the fields, the concentration was ok 10 minutes later and there is disagreement that the field returned to baseline.*

*Patient 1005\_508005 is listed as a repeat field 12 days later which is normal (not captured in the database). The field presented is not a normal right eye field.*

*Patient 127\_006006 is listed as showing worsening ARMD. This does not preclude a drug effect.*

*Patient 131\_105014 is listed as having a normal visual field, but only the central 30 degrees is normal.*

ATTACHMENT 3

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       § 552(b)(5) Deliberative Process

✓       § 552(b)(5) Draft Labeling

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Lisa Malandro  
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## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301) 827-7410

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### DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

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DATE: June 28, 2004

DRUG: LYRICA (pregabalin) 25, 50, 75, 100, 150, 200, 225 and 300 mg Capsules

NDA: 21-446

NDA Code: Type 1P NDA

SPONSOR: Pfizer, Inc.

INDICATION: For the management of neuropathic pain associated with diabetic peripheral neuropathy

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Pfizer submitted NDA 21-446 in support of marketing approval for LYRICA (pregabalin, 25, 50, 75, 100, 150, 200, 225 and 300 mg capsules) for four separate indications: 1) the treatment of pain due to diabetic peripheral sensorimotor neuropathy; 2) the treatment of pain due to post-herpetic neuralgia; 3) the treatment of epilepsy; and 4) the treatment of generalized anxiety disorder (GAD). The application was administratively split into four separate NDAs to facilitate review. The Division had previously determined that applications for products indicated for the treatment of the pain associated with diabetic peripheral neuropathy (DPN) would be considered for priority review due to the severity of this disorder and the absence of any approved products with this indication. The Division has determined that this NDA will receive a priority review, while the application for post-herpetic neuralgia (PHN) will be reviewed on a standard clock. C

Review of the CMC portion of this application was completed by Sharon Kelly, Ph.D. Review of the general pharmacology and toxicology data presented in this application was completed by Jerry Cott, Ph.D and review of the reproductive toxicity and carcinogenicity data was completed by Edward Fisher, Ph.D. A consultation regarding the results of the sponsor's carcinogenicity data was performed by Terry S. Peters, D.V.M. Supervisory reviews were provided by Daniel Mellon, Ph.D., Supervisory Pharmacologist in this division and by Kenneth L. Hastings, Ph.D., Associate Director for Pharmacology and Toxicology, Office of Drug Evaluation II. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by Sue-Chi Lee, Ph.D. A statistical review and evaluation was completed by Ling Chen, Ph.D. A statistical analysis of the dermatologic adverse events in the DPN database was performed by Thomas Permutt, Ph.D., Team Leader for the Biostatistics review group. Consultation on this application was also obtained from the Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products, the Division of Reproductive and Urological Drug Products (DRUDP), the Controlled Substance Staff (CSS), the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Office of Drug Safety (ODS).

The sponsor has submitted four studies (1008-014, 1008-029, 1008-131, 1008-149) in support of efficacy. An additional study, 1008-040, provided no support for efficacy claims. A detailed review of these studies and of the safety of the product was performed by Mwangi Kashoki, M.D. Celia Winchell, M.D. contributed a secondary review for the clinical team. Dr. Jerry Boehm, safety reviewer in the Division of Neuropharmacological Drug Products (DNPD), provided his initial review and conclusions regarding the overall ISS for all four applications to Drs. Kashoki and Winchell, and they have incorporated his findings into their assessments. 1

### *Efficacy:*

**Study 1008-014** (014) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 150 mg or 600 mg and placebo.

Subjects with a diagnosis of diabetic distal symmetrical sensorimotor polyneuropathy for one to five years were enrolled at 29 centers in the U.S. and Canada. The subjects were randomized to pregabalin 150 mg or 600 mg or placebo, in three divided doses per day. Subjects were titrated to these doses starting at 25 mg and increasing by 25-mg increments every 3 days over two weeks. They were then maintained at the fixed dose for four weeks. Subjects recorded their daily pain scores on an 11-point numerical scale in a diary.

Two hundred forty-six subjects were randomized. Twenty-seven subjects did not complete the study.

	<u>Placebo</u>	<u>150 mg</u>	<u>600 mg</u>
Randomized	85	79	82
Completed Study	72	75	72
Reasons for withdrawal:			
Adverse event	4	2	7
Lack of Efficacy	1	0	1
Other*	8	2	2

\*See Dr. Winchell's review, page 10 for breakdown

The primary efficacy outcome was identified as the mean pain score at endpoint, defined as the mean of the last available seven pain scores while on medication. The sponsor's protocol-defined analysis plan called for using the ITT population (all randomized subjects who received at least one dose of study medication) in a comparison of the 150-mg and 600-mg treatment groups, each to the placebo group. The Division prospectively communicated our concern regarding the use of an (last observation carried forward) LOCF analysis to the sponsor. LOCF analyses in studies of analgesic drug products for chronic pain indications frequently overestimate the benefit of the product, as patients who drop out early in the trial due to adverse events, but who had reasonable pain control at the time they dropped out, are counted as successes. The Division proposed a baseline carried forward approach (BOCF). While the sponsor did perform analyses using both LOCF and BOCF approaches, their BOCF analysis was not appropriately implemented. The sponsor only assigned baseline scores for patients who did not complete all study visits and procedures. Thus, subjects who, for example, withdrew from the study before 8 weeks of treatment, but completed the Termination assessments were incorrectly labeled as study completers and their last available mean scores were used in the analysis.

Drs. Chen and Kashoki conducted an analysis using a more rigorous BOCF methodology for imputation of lost data on the ITT population, imputing baseline scores for all subjects who dropped out of the study before the last week. Both of the sponsor's analyses of the primary efficacy outcome data documented statistically significant treatment effects for the 600-mg dose compared to placebo. Dr. Kashoki and Chen's analysis revealed a statistically significant treatment effect for the 600-mg and the 150-mg groups in the pairwise comparisons.

**Reviewer's analysis: Endpoint mean pain scores – Protocol 014**

Time point	N	Placebo Mean (SD)	PGB 150 mg/day Mean (SD)	PGB 600 mg/day Mean (SD)
Baseline*	85	6.90 (1.58)	6.43 (1.32)	6.73 (1.68)
Endpoint**	85	5.92 (2.18)	5.01 (2.10)	4.74 (2.61)
Change	85	-0.98 (1.71)	-1.43 (1.66)	-1.99 (2.12)

\* Baseline = the average of last 7 days prior to randomization

\*\* Endpoint = the average of the last 7 days of the treatment period

The p-values for the pairwise comparisons were 0.0008 and 0.007 for the 600 mg- and 150-mg treatment groups, respectively.

A responder analysis was also performed by the sponsor at the Division's request. Patients with at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The results were consistent with the primary analysis, documenting a statistically significant difference from placebo for the 600-mg group, by both the sponsor's and the Division's methodologies for imputing lost data.

The secondary outcome measures included:

- The Short Form McGill Pain Questionnaire (SF-MPQ)
- A daily diary of sleep interference using an eleven-point numerical rating scale
- The Clinical Global Impression of Change
- The Patient Global Impression of Pain
- The SF-36 Health Survey Questionnaire (SF-36 QOL), and
- The Profile of Mood States (POMS).

The secondary outcome analyses were consistently supportive of the findings for the primary outcome analyses.

**Study 1008-029 (029)** was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 75 mg, 300 mg or 600 mg and placebo.

Subjects with a diagnosis of diabetic distal symmetrical sensorimotor polyneuropathy for one to five years were enrolled at 45 centers in the U.S. The subjects were randomized to pregabalin 75 mg, 300 mg, 600 mg or placebo, in three divided doses per day. Subjects in the 75-mg and 300-mg groups were started on their fixed doses on Day 1 and remained on those doses for five weeks. Subjects in the 600-mg group were titrated to that dose over six days. They were then maintained at the fixed dose for four weeks. Subjects recorded their daily pain scores on an 11-point numerical scale in a diary.

Three hundred thirty-eight subjects were randomized. One patient did not receive study medication and was not included in the ITT population. Thirty-five subjects did not complete the study.

	<u>Placebo</u>	<u>75 mg</u>	<u>300mg</u>	<u>600 mg</u>
Randomized	97	77	82	82
Completed Study	89	67	79	70
Reasons for withdrawal:				
Adverse event	3	2	3	10
Lack of Compliance	1	1	0	0
Lack of Efficacy	2	4	0	0
Other*	2	3	2	2

\*See Sponsor's Table 13, RR 720-04242, 1008-029, p. 45 for breakdown

The primary efficacy outcome was identified as the mean pain score at endpoint, defined as the mean of the last available seven pain scores while on medication. The sponsor's protocol-defined analysis plan called for the using the ITT population (all randomized subjects who received at least one dose of study medication) in a comparison of the 75-mg, 300-mg and 600-mg treatment groups, each to the placebo group. As described above, the Division prospectively communicated our concern regarding the use of an LOCF analysis to the sponsor and performed an additional analysis using a more rigorous BOCF imputation methodology.

Both of the sponsor's analyses of the primary efficacy outcome data documented statistically significant treatment effects for the 300-mg and 600-mg doses compared to placebo. Drs. Kashoki and Chen's analysis also revealed a statistically significant treatment effect for the 300-mg and 600-mg groups in the pairwise comparisons.

**Reviewer's Analysis: Endpoint mean pain scores – Protocol 029**

Time point	N	Placebo	PGB 75 mg/day	PGB 300 mg/day	PGB 600 mg/day
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline*		6.56 (1.57)	6.68 (1.32)	6.09 (1.38)	6.26 (1.44)
Endpoint**		5.30 (2.21)	5.32 (2.34)	3.99 (2.04)	4.06 (2.36)
Change		-1.26 (1.95)	-1.35 (1.94)	-2.10 (1.99)	-2.20 (2.24)

\* Baseline = the average of last 7 days prior to randomization

\*\* Endpoint = the average of the last 7 days of the treatment period

The p-values for the pairwise comparisons were 0.005, 0.003 and 0.4 for the 300-mg; 600-mg and 75-mg groups, respectively.

A responder analysis was also performed by the sponsor at the Division's request. Patients with at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The results were consistent with the primary analysis, documenting a statistically significant difference from placebo for the 300-mg and 600-mg groups, by both the sponsor's and the Division's methodologies for imputing lost data.

The secondary outcome measures included:

- The Short Form McGill Pain Questionnaire (SF-MPQ)
- Mean sleep interference scores
- The Clinical Global Impression of Change
- The Patient Global Impression of Change
- The SF-36 Health Survey Questionnaire (SF-36 QOL), and
- The Profile of Mood States (POMS).

The secondary outcome analyses were generally supportive of the findings for the primary outcome analyses.

**Study 1008-040** (040) was a multicenter, randomized, placebo- and active-controlled, double-blind, parallel-group study comparing pregabalin 600 mg to amitriptyline 75 mg and to placebo.

Subjects with a diagnosis of diabetic distal symmetrical sensorimotor polyneuropathy for at least one year were enrolled at 49 centers in Europe, Australia and South Africa. The subjects were randomized to pregabalin 600 mg or placebo, in three divided doses per day. Subjects were titrated to that dose over two weeks. They were maintained at the fixed dose for six weeks and then tapered off their treatments over one week. (See Titration and Taper Schemes tables, page 65 of Dr. Kashoki's review.) Subjects recorded their daily pain scores on an 11-point numerical scale in a diary.

Two hundred fifty-six subjects were randomized. Two patients did not receive study medication and were not included in the ITT population. Sixty-six subjects did not complete the study.

Placebo                      Pregabalin                      Amitriptyline

Randomized	81	87	88
Completed Study	62	62	64
Reasons for withdrawal:			
Adverse event	4	11	16
Lack of Compliance	2	4	2
Lack of Efficacy	9	7	3
Other*	4	2	2

\*See Sponsor's Table 8, RR 720-30054, 1008-040, p. 63 for breakdown

The primary efficacy outcome was identified as the mean pain score at endpoint, defined as the mean of the last available seven pain scores while on medication. Neither of the sponsor's analyses of the primary efficacy outcome data documented a statistically significant treatment effect for pregabalin compared to placebo.

A responder analysis was also performed by the sponsor at the Division's request. Patients with at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The results were consistent with the primary analysis.

**Study 1008-131** (131) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 600 mg and placebo.

Subjects with a diagnosis of diabetic distal symmetrical sensorimotor polyneuropathy for one to five years were enrolled at 25 centers in the U.S. The subjects were randomized to pregabalin 600 mg or placebo, in three divided doses per day. There was no titration phase and subjects remained on their assigned doses for eight weeks. Subjects recorded their daily pain scores on an 11-point numerical scale in a diary.

One hundred forty-six subjects were randomized and constituted the ITT population. Nineteen subjects did not complete the study.

	<u>Placebo</u>	<u>Pregabalin</u>
Randomized	70	76

Completed Study	62	65
Reasons for withdrawal:		
Adverse event	2	8
Lack of Compliance	1	2
Lack of Efficacy	3	1
Lost to Follow-up	1	0
Other*	1	0

\*See Sponsor's Table 10, RR 720-04452, 1008-131, p. 37 for breakdown

The primary efficacy outcome was identified as the mean pain score at endpoint, defined as the mean of the last available seven pain scores while on medication. The sponsor's protocol-defined analysis plan called for using the ITT population (all randomized subjects who received at least one dose of study medication) in a comparison of the pregabalin-treatment group to the placebo group. As described above, the Division prospectively communicated our concern regarding the use of an LOCF analysis to the sponsor and performed an additional analysis using a more rigorous BOCF imputation methodology.

Both of the sponsor's analyses of the primary efficacy outcome data documented statistically significant treatment effects for the pregabalin group compared to placebo. Drs. Kashoki and Chen's analysis confirmed the sponsor's results.

**Reviewer's Analysis: Endpoint mean pain scores – Protocol 131**

Time Point	Placebo		Pregabalin 300 mg/day	
	N	Mean (SD)	N	Mean (SD)
Baseline	70	6.12 (1.48)	76	6.53 (1.66)
Endpoint	70	5.53 (2.16)	76	4.74 (2.45)
Change		-0.59 (1.47)		-1.79 (2.46)

Baseline = the last 7 days prior to randomization; Endpoint = the last 7 days of the treatment period

The p-value for the pairwise comparison was 0.001.

A responder analysis was also performed by the sponsor at the Division's request. Patients with at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The results were consistent with the primary analysis, documenting a statistically significant treatment effect for pregabalin, by both the sponsor's and the Division's methodologies for imputing lost data.

The secondary outcome measures included:

- The Short Form McGill Pain Questionnaire (SF-MPQ)

- Mean sleep interference scores
- The Clinical Global Impression of Change
- The Patient Global Impression of Change
- The SF-36 Health Survey Questionnaire (SF-36 QOL), and
- The Profile of Mood States (POMS).

The secondary outcome analyses were generally supportive of the findings for the primary outcome analyses.

**Study 1008-149** (149) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 150 mg, 300 mg, or 600 mg and placebo.

Subjects with a diagnosis of diabetic distal symmetrical sensorimotor polyneuropathy for at least one year were enrolled at 58 centers in Europe, Australia and South Africa. The subjects were randomized to pregabalin 150 mg, 300 mg, 600 mg or placebo, in two divided doses per day. Subjects in the pregabalin arms were initiated on 150 mg per day. Subjects in the 300-mg and 600-mg arms were titrated to their final doses over one week. (See Titration Schedule table, page 103 of Dr. Kashoki's review.) Subjects were treated for a total of 12 weeks.

A unique feature of this study was that patients with creatinine clearances of less than 60 mL/min were not excluded. Although the protocol specified that these patients were to be randomized to either the 150-mg, 300-mg or placebo arms, these subjects were actually assigned to all dose arms, but those randomized to the 600-mg arm were treated with 300 mg. This arm was then designated as the 300/600-mg/day group by the sponsor. As noted by the review team, during the study 23 subjects whose creatinine clearance was 30 to 60 mL/min were treated with 300 mg/day and the sponsor designated some of these subjects as members of the 300-mg/day group and others as members of the 300/600-mg/day group in their efficacy analyses. The review team has attempted to address this discrepancy in their evaluation of the efficacy data.

This study was originally designed to enroll a total of 100 subjects who would then be pooled with an identical study performed in the U.S. However, the U.S. study was halted due to the imposition of a partial clinical hold when preclinical carcinogenicity studies documented a finding of hemangiosarcomas in pregabalin-treated animals. The protocol was amended to stipulate enrollment of 352 subjects and a revised statistical analysis plan omitted the earlier expectation for pooling of data with a U.S study. In November of 2001, regulatory decisions in some participating countries resulted in a change in the inclusion/exclusion criteria that required the premature discontinuation of 11 subjects from the study. These subjects were replaced in order to reach the desired sample size and were excluded from the efficacy analyses. The sponsor's Modified-ITT (MITT) population omits these 11 patients.

Subjects recorded their daily pain scores on an 11-point numerical scale in a diary.

Three hundred ninety-six subjects were. Seventy-seven subjects did not complete the study.

	<u>Placebo</u>	<u>150 mg</u>	<u>300 mg</u>	<u>300/600 mg</u>
Randomized	97	99	99	101
Completed Study (MITT)	79	82	79	78
Reasons for withdrawal:				
Adverse event	3	5	11	13
Lack of Compliance	0	0	0	1
Lack of Efficacy	11	8	5	3
MoH/EC* decision	3	2	3	3
Other**	0	2	1	3

\* Ministry of Health/Ethics Committee

\*\* See Sponsor's Table 9, RR 720-30080, 1008-149, p. 69 for breakdown

The primary efficacy outcome was identified as the mean pain score at endpoint, defined as the mean of the last available seven pain scores while on medication. The sponsor's protocol defined (after Amendment 3) analysis plan called for the using the MITT population in a comparison of the pregabalin-treatment groups to the placebo group. As described above, the Division prospectively communicated our concern regarding the use of an LOCF analysis to the sponsor and performed an additional analysis using a more rigorous BOCF imputation methodology.

Both of the sponsor's analyses of the primary efficacy outcome data using LOCF for the ITT and the MITT populations documented a statistically significant treatment effect for the 300/600-mg/day group compared to placebo. The treatment effects for the 300-mg and 150-mg groups compared to the placebo group were not statistically significant. The sponsor's analyses using BOCF found none of the treatment groups to have a statistically significant treatment effect compared to the placebo group. Drs. Kashoki and Chen's performed an analysis with BOCF on the MITT population, employing the modifications described in the studies above. In addition, they reassigned the 13 subjects in the 300/600-mg group who had low creatinine clearances and who were treated with 300 mg/day to the 300-mg group for this analysis. This analysis found that none of the treatment groups had a statistically significant treatment effect when compared to the placebo group.

A responder analysis was also performed by the sponsor at the Division's request. Patients with at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The results document an apparent increase in the responder rate for the patients treated with 600 mg per day when assigned to treatment group based on either the sponsor's or the Agency's analyses. Importantly, when the patients are stratified by creatinine clearance, the patients in the 300-mg/day arm respond to treatment less frequently than even the placebo-treated patients.

% of Subjects with Change from Baseline Pain of  $\geq 50\%$ , BOCF analysis, Study 1008-149

Creatinine clearance	Proportion of Responders (%)			
	Placebo	150 mg/day	Pregabalin 300 mg/day	600 mg/day
> 60 mL/min	25	30	28	36
$\leq 60$ mL/min	33	25	22	-

The secondary outcome measures included:

- The Short Form McGill Pain Questionnaire (SF-MPQ)
- Mean sleep interference scores
- The Clinical Global Impression of Change
- The Patient Global Impression of Change
- Medical Outcomes Study – Sleep Scale
- The SF-36 Health Survey Questionnaire (SF-36 QOL), and
- EuroQol Health State Profile – VAS AUC score and single index value score

The secondary outcome analyses were generally supportive of the sponsor's findings for the 300/600-mg/day group in their primary outcome analyses.

### *Clinical Safety:*

#### Exposure

A total of 803 subjects were exposed to pregabalin in clinical pharmacology studies. A total of 8666 patients were exposed to pregabalin in Phase 2 and 3 studies for all indications. In the DPN program, a total of 1413 patients received at least one dose of

pregabalin. Two hundred eighty-nine DPN subjects were treated with pregabalin 600 mg/day for at least 6 months, and 201 for at least one year.

### Deaths

A total of 55 deaths were reported in the ISS. Seventeen of these deaths occurred in the DPN population. Most deaths were due to cardiac disease and occurred with a frequency that would be expected in this patient population. Sudden unexplained death occurred primarily in the epilepsy population and is consistent with that unusual but not rare cause of mortality in epileptic patients. While the mortality risk was clearly higher in the DPN and PHN compared to the epilepsy and GAD populations, most of the deaths in the former two patient groups occurred in patients over 65 years of age. Per the clinical review team, none of the deaths appeared to be clearly associated with pregabalin exposure.

One death in a DPN patient could have been related to treatment with pregabalin. This 72-year-old woman had a family history of leukemia and was found to have a low platelet count on Day 320 of treatment with pregabalin. Pregabalin was discontinued, but then restarted on Day 335. On Day 356, the patient was found to have developed pancytopenia and myelodysplasia, and on Day 383 the pregabalin was stopped a second time when she was again found to have a low platelet count. On Day 867 she was diagnosed with myelodysplastic syndrome and she died on Day 941 after a total exposure to study drug of 420 days. Although this patient died one and a half years after treatment with pregabalin was discontinued, it is possible that the study medication was an inciting or promoting factor in the illness that led to her death. However, myelodysplastic syndrome is not rare in the elderly.

In the 120-day Safety Update, an additional 13 deaths were reported, 8 of which occurred during the completed trials and 5 that occurred in on-going trials. None of the deaths were without possible alternate cause, except for a case of accidental head injury following a fall. However, that patient was elderly, and had a history of falls.

### Discontinuations Due to Adverse Events

Approximately 13% of subjects in the controlled-trials overall database and 9% of subjects in the controlled-trials DPN database discontinued due to an adverse event. During the DPN-controlled trials, approximately 4% of placebo-treated subjects and 9% of pregabalin-treated subjects discontinued due to adverse events. Only dizziness, somnolence and headache were cited with a frequency of greater than 1% subject discontinuation in the pregabalin-treated subjects in the DPN-controlled trials. Of note, however, asthenia, blurred vision (termed "amblyopia" by the sponsor), dry mouth, nausea, confusion, peripheral edema, accidental injury, infection, ataxia, tremor, constipation, diarrhea, incoordination, and abnormal thinking did result in subject discontinuation slightly more often in the pregabalin-treated compared to the placebo-treated patients.

### Serious Adverse Events

Eight percent of pregabalin-treated patients in the overall database experienced one or more serious adverse events. The "Overview of SAEs by Indication" table on page 40 of Dr. Winchell's review breaks down the incidence of serious adverse events occurring in the various DPN-patient populations. In the all controlled-trials database, the incidence of serious adverse events was approximately equal for the pregabalin- and placebo-treated subjects. Accidental injury was the only serious adverse event that occurred with an incidence of greater than or equal to 1% in the all-uncontrolled studies database. Accidental injury occurred with a slighter higher frequency in the pregabalin-treated compared to the placebo-treated subjects in the all-controlled trials database. In the combined database for all studies, the most common serious adverse events were accidental injury, pneumonia, chest pain, congestive heart failure, myocardial infarction, and angina pectoris. Each of these occurred with a frequency of less than 1%.

In the DPN-controlled clinical trials, the following serious adverse events occurred with slightly higher frequency in the pregabalin- compared to the placebo-treated subjects: chest pain, accidental injury, infection, pneumonia, congestive heart failure, myocardial infarction, angina pectoris, cerebrovascular accident, dyspnea, hypoglycemia, and vomiting. Approximately 17% of pregabalin-treated patients in the combined controlled and uncontrolled-DPN clinical studies database experienced at least one serious adverse event. Of these events, pulmonary fibrosis, leukemoid reaction, macrocytic anemia, edema, acute renal failure, abscess and cellulitis were assessed as possibly related to study drug exposure by the clinical review team, though without an established connection. Each of these events occurred with a frequency of less than 1%.

### Common Adverse Events

Based on the clinical team's assessment of the common adverse events occurring in the pregabalin-treated subjects in the DPN placebo-controlled trials, it appears that events associated with the nervous system were the most common. These included: dizziness (21%) and somnolence (12%), as well as confusion, abnormal thinking, euphoria, gait abnormalities, incoordination, tremor, ataxia and vertigo. Another frequently noted event was edema, occurring in 13% of subjects. Blurred vision (coded as "amblyopia") and vision abnormalities occurred with greater frequency in the pregabalin-treated patients, as did dry mouth, constipation and dyspepsia.

### Vascular Neoplasms

Due to the preclinical finding of hemangiosarcomas in the preclinical carcinogenicity studies, Dr. Kashoki reviewed the clinical database for vascular neoplasms. There was one event coded as "angioleiomyoma," one as "angioma," and one as "cherry angiomas." However, additional documentation on these events provided by the sponsor did not suggest causality.

## Dermatopathy

Based on the preclinical findings of severe dermatopathy in rats and monkeys, and concern regarding poor wound healing and an increased occurrence of skin ulcers in the diabetic patient population, Dr. Kashoki reviewed the database for dermatologic adverse events. For both the overall and the DPN databases, it was difficult to distinguish whether higher incidences of dermatologic adverse events in the pregabalin-treated subjects was a direct effect of drug or an effect related to longer time on treatment for DPN subjects in open-label trials. In the controlled trials for the DPN program, skin ulcers occurred with a similar frequency in the pregabalin- and the placebo-treated subjects. In the combined database for the DPN program, skin ulcers occurred with a higher frequency in subjects taking greater than or equal to 300 mg per day, with an apparent dose dependency. However, an analysis of ulcer-free survival time in this population performed by Dr. Permutt suggested that differences in time on study accounted for the observed effect.

## Ophthalmologic Adverse Events

Ophthalmologic adverse events appeared to occur more frequently in pregabalin-treated than placebo-treated subjects. Due to the clear vulnerability of the diabetic population, Dr. Wiley Chambers, Deputy Director of the Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products, was consulted and reviewed the ophthalmologic adverse event profile, as well as the data available from visual field testing and visual acuity testing that had been included in some of the clinical trials. Dr. Chambers judged the testing program to be insensitive to minor changes and unlikely to detect a difference across treatments due to methodological flaws. Nevertheless, he noted an effect of pregabalin on both visual field loss and on impairment in visual acuity.

Visual acuity and visual field changes were more commonly seen in the pregabalin group than the placebo group. This was particularly true for visual field changes at the 300-mg dose and visual acuity changes at the 600-mg dose. Dr. Chambers found that it was not possible to identify a specific pattern of visual acuity or visual field defects and that the changes were relatively small. In addition, in most cases, the changes only affected the visual function reserve of individual patients. He concluded that, "Relatively few of the changes would significantly affect typical activities of daily living."

In his consultation dated April 2, 2004, Dr. Chambers also stated:

From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling identifies the potential of pregabalin to cause decreased visual acuity and decreased fields of view (i.e., visual fields).

Dr. Chambers recommended additional adequate and well-controlled studies to be performed during Phase 4, and risk management steps that would include short-term, six-month, and long-term ophthalmologic testing for patients treated with pregabalin.

### Glycemic Control

Dr. Kashoki examined the database for evidence of an effect of pregabalin on glycemic control, due to the vulnerability of the diabetic population. Her evaluation did not find any specific effect related to pregabalin exposure.

### Reproductive Toxicity

As animal studies revealed reproductive toxicity in males, the Division of Reproductive and Urologic Drug Products was consulted to assess the sponsor's clinical study that had been performed in human volunteers and that had been designed to evaluate the effect of the study drug on reproductive function. In that consultation, Dr. Olivia Johnson concluded that, due to the study design and the small sample size, the study did not provide reasonable reassurance that pregabalin has no adverse effect on human reproductive function. Dr. Johnson recommended that a further clinical trial should be performed during Phase 4.

### Edema and Weight Gain

Dr. Kashoki thoroughly assessed the ISS database in regard to cases of edema, a commonly noted adverse event in the pregabalin-treated subjects and a clinical event that could be of concern in the diabetic population. The incidence of edema in all controlled trials was 6% in the pregabalin-treated subjects compared to 2% in the placebo-treated subjects. The incidence was highest in the DPN and PHN subjects, 9% and 12%, respectively.

Weight gain was also noted by the clinical review team to have occurred more frequently in pregabalin-treated subjects. Across all of the controlled studies, the incidence for pregabalin-treated subjects found to have a weight gain from baseline to anytime during treatment was 13% compared to 2% for the placebo-treated subjects. In addition, for subjects with a normal BMI at baseline, the incidence of an increase in BMI during treatment was 5% for those treated with pregabalin compared to 2% for those administered placebo. In the DPN controlled trials, 8% of the pregabalin-treated subjects compared to 2% of the placebo-treated subjects had an increase in weight from baseline to anytime during treatment. The increase in weight gain did not appear to be dose-related. While the sponsor found that, for the majority of subjects, the amount of weight gain was 10% of baseline or less, this amount of weight gain could still result in a clinically significant effect, particularly in diabetic patients. The occurrence of edema was not highly correlated with the occurrence of weight gain.

### ECG Findings and QT-Interval Changes

Review of the available ECG data collected during the clinical studies did not reveal clinically relevant concerns regarding cardiac arrhythmia or QT-interval prolongation.

However, no formal clinical pharmacology or in vitro studies of QT prolongation were performed during the development program.

#### Platelet Abnormalities

Across all controlled studies, pregabalin-treated subjects experienced a mean decrease in platelet count of  $10 \times 10^3/\mu\text{L}$  compared to  $0.3 \times 10^3/\mu\text{L}$  for the placebo-treated subjects. The mean changes ranged from  $-5 \times 10^3/\mu\text{L}$  in the 150-mg treated subjects to  $-12 \times 10^3/\mu\text{L}$  in the 450-mg treated subjects. Across all controlled and uncontrolled studies, pregabalin-treated subjects experienced a mean decrease in platelet count of  $5 \times 10^3/\mu\text{L}$ . The mean decrease in platelet count for pregabalin-treated subjects in the DPN population was  $10 \times 10^3/\mu\text{L}$ .

Across all controlled trials, 3% of pregabalin-treated subjects and 2% of placebo-treated subjects experienced a "clinically significant decrease in platelets," defined as 20% below baseline and less than  $150 \times 10^3/\mu\text{L}$ . Platelet counts below  $100 \times 10^3/\mu\text{L}$  occurred in less than 1% of both placebo- and pregabalin-treated subjects. For most of the subjects with low platelet counts, the counts were transient and/or below normal at baseline. Review of 120 subjects with platelet counts equal to or less than  $100 \times 10^3/\mu\text{L}$  performed by Dr. Boehm did not reveal a clear association between the decrease and development of bleeding abnormalities.

A clinical study was performed by the sponsor to assess the effect of pregabalin on platelet function due to their attribution of the hemangiosarcomas found in the preclinical studies to a species-specific effect on endothelial cells, platelet activation and platelet aggregation. This study in volunteer subjects did not detect any effect.

#### Creatinine Kinase Elevation

Across all controlled studies, pregabalin-treated subjects experienced a mean increase in creatinine kinase (CK) from baseline to endpoint of 10 U/L compared to 5 U/L for the placebo-treated subjects. Across all controlled and uncontrolled studies, pregabalin-treated subjects experienced a mean increase in CK of 12 U/L. The mean increase from baseline to maximum value across all controlled studies was 60 U/L in the pregabalin group compared to 28 U/L in the placebo group. For the controlled DPN studies, the mean increase from baseline to maximum value was 32 U/L for the pregabalin group compared to 13 U/L for the placebo group.

Dr. Boehm analyzed the CK mean changes in the pregabalin group by study visit for the epilepsy controlled trials and found that these changes, relative to the placebo group, were present early, varied over the course of the study, and did not suggest a dose response. Analysis of outlier data did not reveal clinically significant differences in high CK levels between the pregabalin and the placebo subjects.

Dr. Boehm also assessed the 13 subjects in the overall database who had CK levels greater than five times the upper limit of normal (ULN) and who also had a recorded adverse event suggestive of myopathy. Of these 13 subjects, 6 had abnormalities suggestive of a relationship to pregabalin treatment, although 3 of those 6 experienced resolution of their symptoms during continued treatment with pregabalin. Two subjects were discontinued due to CK elevation greater than five times the ULN. There did not appear to be any subject with clinically relevant changes in renal function related to elevation of CK levels. There was no clear evidence of renal failure or rhabdomyolysis associated with CK elevation.

### *Nonclinical Safety:*

#### Dermatopathy

Severe dermatologic abnormalities were noted, primarily involving the tails of pregabalin-treated animals (both rats and monkeys). These abnormalities included hyperkeratosis, acanthosis, inflammation, hemorrhage, fibrosis, necrosis, ulcers, scab formation, and cellular infiltrates. These changes occurred at human equivalent doses (HED) that are 3 times the maximum proposed human dose of 300 mg/day.

#### Hematologic Changes

In mechanism studies in the mouse, pregabalin was associated with an increase in platelet counts, altered platelet morphology, and increased megakaryopoiesis. These effects were frequently evident at HEDs that are 2 times the maximum proposed human dose. In contrast, platelet counts were decreased in rats at comparable doses, i.e., at a dose of 900 mg/kg for up to 18 months. There was no evidence of increased platelet activation in monkeys given 500 mg/kg for up to 69 weeks.

#### Reproductive Changes

Histological changes in the epididymis of rats were noted at a HED that is 3 times the maximum proposed human dose. In monkeys, histological abnormalities were noted in the epididymis and testes in isolated animals in a 4-week study. However, no significant histological findings were noted in a 13-week study at doses up to 500 mg/kg/day or 13 times the maximum proposed human dose of 300 mg/day. In male fertility and early embryonic development studies performed in rats, marked reproductive toxicity at 7 times the maximum proposed human dose was manifested as reduced fertility, increased days to mating, decreased sperm counts and motility, abnormalities in sperm morphology, decreased implantations, increased preimplantation loss, fetal body weight decrease, and increased malformations including anal atresia, eye defects and skeletal abnormalities. Although the sponsor contends that these findings are not clinically relevant as there were no malformations that were dose-related and all of the findings were similar to historical controls, Dr. Fisher concluded that any increase in malformations should be considered a teratogenic response.

In a female fertility study, pregabalin treatment resulted in disruption of the estrus cycle and an increase in the number of days to mating. High doses also appeared to decrease the fertility index. Peri- and post-natal development studies in the rat revealed maternal toxicity including abnormalities in offspring survival, growth, behavior and reproductive function at 8 times the maximum proposed human dose of 300 mg/day.

#### Hemangiosarcomas

An increased incidence of hemangiosarcomas was noted in a carcinogenicity study in one strain of mice at a human exposure ratio of 2, based on a maximum dose of 300 mg/day. This finding was confirmed via studies in a second strain of mice. This finding was not noted in a carcinogenicity study in rats. The sponsor's assessment of this finding is that the mouse model is not the most appropriate species for human risk assessment. They based this conclusion on extensive studies that characterized the effects of pregabalin on the cells most likely to be involved in this type of tumor production. They have proposed that:

- Compared to rats and humans, mice have a higher  $pO_2$  in arterial blood and a lower  $pO_2$  in venous blood, consistent with a higher metabolic rate in mice.
- Pregabalin produces respiratory depression in mice leading to a relative and uncompensated alkalotic state.
- The resulting tissue hypoxia and chronic relative alkalosis stimulate an increased incidence of hemangiosarcomas via effects on platelets, megakaryocytes and endothelial cells.

However, the toxicology review team has determined that, although the sponsor's hypothesis represents a plausible explanation for the increased incidence of hemangiosarcomas, inconsistencies exist in the data and, therefore, the results remain inconclusive.

Dr. Daniel Mellon, the team leader for the pharmacology/toxicology review group, has also expressed concern that diabetic patients are increasingly being treated with peroxisome proliferator-activated receptor compounds (PPAR $\gamma$ ) that have been associated with the development of hemangiosarcomas in mice. He has hypothesized that exposure to both PPAR $\gamma$  compounds and pregabalin could result in an increased incidence of hemangiosarcomas in diabetic patients.

The nonclinical review team has recommended that this application is not approvable based on the toxicity profile demonstrated in the animal studies. However, Dr. Hastings, in his supervisory memo states:

Having read the reviews and considered the recommendation for non-approval, I do not concur. The dermatopathy findings are certainly of concern, especially given the indication

sought by the sponsor... There are two factors that should be taken into consideration, neither of which should be addressed in the evaluation of nonclinical studies: (1) the apparent lack of an increased incidence of similar dermatopathy in clinical trials, and (2) the compelling need for the indication. Although the hemangiosarcoma findings are also of concern, the potential benefit of this drug outweighs the risk considerations. I therefore recommend that this application be approved.

### ***Biopharmaceutics:***

Drs. Lee and Nallani have concluded that this application is approvable. However, they recommend that the sponsor [redacted] in Phase 4: [redacted] that includes an adequate representation of women and elderly subjects; and, an in vitro study in primary cultures of human hepatocytes to address CYP induction by pregabalin.

### ***Chemistry, Manufacturing and Controls:***

The CMC review team has recommended approval of this application. A satisfactory cGMP compliance recommendation was received from the Office of Compliance on June 22, 2004. The sponsor has agreed to the following post-marketing commitments and other provisions:

- To test the first three lots of pregabalin at the Ringaskiddy plant for [redacted] an impurity which is a potential carcinogen and which could be found at unacceptable levels [redacted] in the drug manufacturing process at this site.
- To submit a prior-approval supplement revising the drug substance specifications to include a limit of not more than  $-\text{?PM}$  for [redacted] if the above results indicate the levels to exceed  $-\text{?PM}$ .
- Adequate documentation of the batch reference for [redacted] for the regulatory starting material in all future manufacturing.
- A retest interval of [redacted] for the drug substance that is extendable through annual report based on the accrual of additional satisfactory real time data.
- Establishment of a limit of no less than  $— \text{ ng/mL}$  for the [redacted] drug substance, to be reported in the next annual report.
- Revision of the post-approval stability protocol for the drug product to include semi-annual testing in the first and second year of marketing.

the review team has determined that the currently available data support a shelf life of only for the 25-mg, 50-mg, 75-mg, and 100-mg strengths.

#### *Nomenclature:*

The sponsor's proposed Tradename, LYRICA, was found to be acceptable by both the ODS and DDMAC review teams.

#### *Abuse Liability, Withdrawal Phenomena and Overdose:*

The abuse liability of pregabalin was evaluated by CSS. They concluded that pregabalin has a similar degree of abuse liability to diazepam, and that control under Schedule IV of the Controlled Substances Act should be recommended to the Drug Enforcement Administration. CSS will prepare an Eight-factor Analysis, as required, and the product may not be marketed, even if approved, until the DEA has completed consideration and implementation of any scheduling action. However, the sponsor has submitted a Formal Dispute Resolution request to the Office of the Center Director, and this issue remains under discussion within that Office.

Discontinuation-emergent signs and symptoms (DESS) were more common in pregabalin than placebo-treated subjects across the entire database. However, in one DPN study (Study 1008-040), which featured a one-week taper at the end of eight weeks of treatment, DESS occurred in 11% of pregabalin-treated subjects compared to 16% of placebo-treated subjects and 14% of amitriptyline-treated subjects. CSS determined that subjects who abruptly discontinue pregabalin treatment over a short duration commonly experienced insomnia, headaches, nausea and diarrhea. They concluded that this constellation of symptoms represented a withdrawal syndrome indicating the presence of physical dependence.

In addition, CSS noted that euphoria was reported as an adverse event in the clinical trials at a rate consistently higher in pregabalin-treated compared to placebo-treated subjects across all indications. The highest rates of euphoria (5 to 12 % in pregabalin-treated subjects compared to 1% in placebo-treated subjects) occurred in the GAD studies.

Pregabalin also produced self-administration in rhesus monkeys at some infusion doses during initial access to the drug. CSS concluded that this data supported their determination that pregabalin produces reinforcing effects.

Adverse events associated with overdoses (intentional or accidental) included accidental injury, headache, asthenia, dizziness, somnolence, ataxia, blurred vision, confusion, peripheral edema, and diplopia. No deaths resulted from overdose. The maximum reported overdose was 15,000 mg and resulted in no consequences.

### *Discussion:*

I concur with the clinical review team that the sponsor has provided substantial evidence of efficacy for pregabalin at doses of 300 to 600 mg per day in the treatment of the pain associated with diabetic peripheral neuropathy for up to eight weeks. I also agree that the data do not support any added benefit of the 600-mg dose over the 300-mg dose. However, Study 014 did find a statistically significant treatment effect for the 150-mg dose based on the Division's analysis and this dose should also be considered as effective. It will be important to note in the product labeling that durability of effect for pregabalin has not been established beyond eight weeks.

Drs. Kashoki and Winchell have recommended against approval of this application due to the numerous toxicities seen in the non-clinical and clinical studies, and their conclusion that the risk to benefit ratio is unfavorable. I agree that this product appears to be associated with toxicities that are of clinical concern and that these toxicities are particularly relevant to the diabetic patient population. While these findings are relevant, I do not find the data regarding most of these toxicities to be compelling. Some of the toxicities noted in the animal studies did not appear in the clinical studies (e.g., dermatopathy). Other toxicities noted in the clinical trials appeared to be detectable with appropriate monitoring and to be reversible upon discontinuation of the drug (e.g., ophthalmologic changes and peripheral edema). However, these potential adverse effects should be clearly defined in the product labeling, with appropriate recommendations for monitoring, as well as treatment and/or drug discontinuation. I also agree with Dr. Chambers that a more robust clinical evaluation of the ophthalmologic toxicity of pregabalin should be performed in Phase 4 to better inform the labeling.

It is not possible to establish the relevance of the animal carcinogenicity findings to patients in relatively short-term clinical studies. However, these findings can be carefully described in the product labeling allowing prescribers and patients to assess the value of treatment compared to the potential risk associated with that treatment. Successful treatment of the severe and often incapacitating pain experienced by patients with DPN can only be fairly weighed against the risk of exposure to a possible carcinogen by the patients experiencing that pain, and by their families and their health care providers.

The reproductive toxicity noted in the animal studies does remain concerning, especially in light of the inadequate clinical evaluation performed during product development. However, the potential effects on the reproductive system can also be described in the product labeling, allowing patients and prescribers to make an informed risk to benefit assessment. Additionally, further clinical evaluation in Phase 4 should be undertaken by

the sponsor as soon as possible to allow for a more complete understanding of any reproductive toxicity in humans.

I concur with Dr. Hastings recommendation for a Phase 4 study

It is possible that these effects would not have been detected in the clinical studies, and immunosuppression could be particularly detrimental to diabetic patients and could be monitored for during long-term treatment.

I do not agree that further animal studies would provide useful data in regard to the dermatopathy noted in the non-clinical studies performed to date. With a safety database of over 9000 patients, and no signal of dermatologic toxicity, abnormal wound healing or an increase in skin ulceration in diabetic patients noted in those studies, further animal studies would be redundant and uninformative. Nevertheless, it would be useful to describe the animal findings in the product labeling. I also do not agree with Dr. Mellon's recommendation for a Phase 4 interaction study between pregabalin and PPAR $\gamma$  agonists, as the currently approved PPAR $\gamma$  agonists have not demonstrated any propensity to cause hemangiosarcomas in animals. Should PPAR $\gamma$  agonists with a clear propensity to cause hemangiosarcomas in animals be approved, an interaction study would be appropriate in order to provide informed labeling for pregabalin.

The labeling should, however, caution prescribers in regard to the potential for both pregabalin and the PPAR $\gamma$  agonists to cause peripheral edema, possibly resulting in an additive or synergistic effect that would clearly impact diabetic patients. Cautions regarding weight gain and peripheral edema caused by pregabalin alone should also be included in the product labeling.

I concur with the biopharmaceutics team's recommendation for Phase 4 studies to

the potential for pregabalin to induce CYP metabolism in an in vitro study.

Diabetic peripheral neuropathy is frequently a severe and incapacitating disorder due to the profound and unrelenting pain that these patients experience. As there are no approved drug products currently available to treat DPN, it is clearly in the best interests of patients suffering from DPN to provide a rationale pharmacological treatment, if possible. While pregabalin does present a number of concerns related to its potential for toxicity, the overall risk to benefit ratio supports the approval of this product, with appropriate labeling and with Phase 4 studies that will better elucidate those toxicities and their possible impact on patients.

***Action recommended by the Division:***

I recommended that this application be approved with appropriate labeling and with the following Phase 4 commitments:

NDA 21-446 Division Director's Summary Review and Recommendation for Approval

22

Pregabalin  
June 28, 2004

1. Additional adequate and well-controlled clinical studies to assess the ophthalmologic toxicity of pregabalin
2. An adequate and well-controlled study of human reproductive toxicity
3.  J
4.  J
5. An in vitro study of pregabalin's propensity to induce CYP-enzyme metabolism.

Bob A. Rappaport, M.D.  
Director  
Division of Anesthetic, Critical Care and Addiction Drug Products  
Office of Drug Evaluation II, CDER, FDA

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Bob Rappaport  
6/28/04 06:39:54 PM  
MEDICAL OFFICER

## MEMORANDUM OF TELECONFERENCE

DATE: June 14, 2004

APPLICATION NUMBER: NDA 21-446, LYRICA (pregabalin) Capsules

BETWEEN:

Name: EMEA representatives

AND

Name: Lisa Malandro, Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products,  
HFD-170

SUBJECT: NDA 21-446 Pregabalin, Discussion with EMEA

A teleconference was held on March 24, 2004, between representatives of the FDA and the EMEA in order to discuss the pending drug application for pregabalin. Particularly, the Division of Anesthetic, Critical Care and Addiction Drug Products desired to discuss key safety issues with the EMEA reviewers who had recently recommended the drug for marketing. Following introductions, Dr. Rappaport began the teleconference by explaining that the Division is currently reviewing the application for two indications (neuropathic pain due to diabetic peripheral neuropathy and neuropathic pain due to post-herpetic neuralgia) and noting that the EMEA reviewed the application with respect to a broader claim of neuropathic pain. Four safety issues were identified for discussion including: carcinogenicity and dermatopathy identified in the preclinical studies, visual acuity and visual field deficits identified in the clinical trials and abuse potential. A summary of the discussion relating to each of these issues follow.

**Carcinogenicity**-The EMEA reviewers stated that they felt that the Sponsor's package of mechanistic studies supported the Sponsor's claim that incidences of hemangiosarcoma are species specific and do not have a correlation to other rodents, monkeys or man. The EMEA also stated that the evaluation of the mechanism of platelet dysfunction detected no effect. Dr. Cott stated that the data varied between the two strains of mice and that the Sponsor's correlation was inconclusive.

**Dermatopathy**-Dr. Rappaport stated that the FDA does not feel that, based on the clinical study data, this issue would interfere with approval of the drug, nor will it be treated as a major labeling issue. The EMEA agreed with the Division's interpretation of the data.

**Visual Acuity and Visual Field Deficits**-Dr. Rappaport stated that, due to the increased incidence of visual changes, the Division is considering adding a warning to the label to recommend routine monitoring and discontinuation of the drug if effects on visual acuity or visual field become apparent. The EMEA stated that they, too, evaluated these data. Based upon the outcome of the preclinical studies (no effect), the confounding factors in the clinical studies and the large amount of clinical data, the EMEA recommended that this finding be followed-up

by Periodic Safety Update Reports (PSUR). PSUR reports would be submitted to the EMEA every six months for the first two years and annually for the following six years. The EMEA did not recommend a post-marketing study due to the lack of a pattern in the current, extensive database. Dr. Rappaport agreed that this issue should be monitored post-marketing.

**Abuse Liability**-Dr. Rappaport stated that the Agency's assessment was that pregabalin has a similar effect as benzodiazepines, that there is an increased rate of euphoria in the database (particularly in generalized anxiety disorder patients), and that the recommendation to the Drug Enforcement Agency was to schedule this drug. The EMEA stated that they felt that the monkey self-administration study did not show an abuse effect and was reassuring to them. Additionally, the EMEA reviewers stated that the symptoms of withdrawal do not indicate an addiction. In the single-dose trial, pregabalin did not cause the same response as diazepam. It was clarified that the EMEA did not receive or review the data from the generalized anxiety disorder (GAD) studies. Dr. Winchell clarified that there was an increase in euphoria of approximately 12% in the GAD population.

/s/

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Lisa Malandro  
Regulatory Project Manager

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/s/

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Lisa Malandro  
6/16/04 05:48:03 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

8/4/04

NDA 21-446

NDA 21-723

NDA 21-724

L J

CP Pharmaceuticals International C.V.

Attention: Jonathon Parker, R.Ph., M.S.

Global Regulatory Leader, Regulatory Strategy, Worldwide Regulatory Affairs

c/o: Pfizer Inc.

235 East 42<sup>nd</sup> Street

New York, NY 10017

Dear Mr. Parker:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lyrica (pregabalin) Capsules.

We refer also to your July 16, 2004, request for formal dispute resolution received on July 20, 2004. Please note that the receipt date of the official submission of your request was incorrectly stated in our acknowledgement letter of July 23, 2004. The appeal concerned the scheduling recommendation by the Controlled Substance Staff (CSS) to schedule pregabalin under the Controlled Substance Act as a Schedule IV product.

We also refer to our communication on August 4, 2004, when we contacted you to confirm that the data used to support the arguments in your appeal had already been provided to us via submission to the administrative file. The minutes from that teleconference are attached. We acknowledge your responses to our inquiry on August 6, 12 and 13, 2004.

In your August 6, 2004, communication, you indicated that individual patient data for Study 1008-098 had not been submitted to your NDAs. Therefore, as discussed with you on August 13, 2004, your appeal relies upon new, unreviewed information, and does not qualify as a formal dispute resolution appeal. We agree that the individual patient data from this study is critical and could potentially affect our interpretation of Study 1108-098, and therefore could impact the recommendation for scheduling made by CSS.

We further acknowledge that this information has now been submitted to your NDAs and will be reviewed in an expeditious manner. If, after review of the information by the CSS, the issue is still not resolved to your satisfaction, you may appeal the matter to the Center Director.

Any new request for formal dispute resolution should be sent to Kim Colangelo, Formal Dispute Resolution Project Manager at:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Mail Code HFD-020  
5515 Security Lane  
Rockville, MD 20852

If you have any questions, call Ms. Colangelo at (301) 594-3937.

Sincerely,

*(See appended electronic signature page)*

Douglas C. Throckmorton  
Acting Deputy Director  
Center for Drug Evaluation and Research

## MEMORANDUM OF TELECON

DATE: August 4, 2004

APPLICATION NUMBERS: NDA 21-466, NDA 21-723, NDA 21-724 C  
Lyrica (pregabalin) Capsules

3

BETWEEN:

Name: Jonathan Parker, R.Ph., M.S., Global Regulatory Leader  
Representing: Pfizer Inc

AND

Name: Kim Colangelo, Associate Director for Regulatory Affairs  
Office of New Drugs  
Douglas C. Throckmorton, M.D., Acting Deputy Director  
Center for Drug Evaluation and Research

SUBJECT: Pending request for formal dispute resolution

The purpose of this conference call was to confirm that the data to support arguments made in Pfizer's request for formal dispute resolution had been previously submitted to the administrative file and did not constitute new data. Pfizer is disputing the recommendation by Controlled Substance Staff (CSS) to schedule pregabalin under the Controlled Substances Act as a Schedule IV product. Pfizer has countered that the data used to support the CSS recommendation for scheduling were selective and contradictory. The source of data supporting Pfizer's appeal regarding CSS interpretation of data in three areas was discussed: adverse events of "euphoria" in clinical trials, use in recreational sedative abusers, and the comparative abuse liability of gabapentin.

### Euphoria

Reference to individual patient data was requested from the two studies cited in the appeal to test within-subject reproducibility of "euphoria" (Studies 1008-088 and 1008-082). Pfizer stated they would confirm that the data had been submitted to the NDAs, and provide the references (links) to the location of the data in the electronic submission. Pfizer did not believe that the individual data had been included in the abuse liability section of the NDAs.

### Recreational Sedative Abusers

Reference to individual patient data was requested for the human abuse liability study (Study 1008-098). Pfizer stated they would confirm that the data had been submitted to the NDAs, and provide the reference (link) to the location of the data in the electronic submission.

### Abuse liability of comparable drugs

Pfizer cited postmarketing data with gabapentin (which is not a scheduled product). Pfizer asserts gabapentin is a suitable comparator to pregabalin based on shared chemical properties and pharmacological action. An explanation of where and how the reported postmarketing data were generated as well as the actual supporting data was requested.

Next Steps

Pfizer agreed to submit this response via email (with official submission to follow) given the approaching response due date for this appeal. Pfizer noted that the third request may take additional time; therefore, all parties agreed that the data should be submitted as it was made available to facilitate timely review.

If all of the data noted above have already been submitted to the NDAs, then Dr. Throckmorton would likely grant Pfizer's request for a face-to-face meeting to discuss the data in an effort to resolve the dispute.

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/s/

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Doug Throckmorton  
8/24/04 09:34:22 AM

Executive CAC  
December 12, 2000

Committee: Joseph DeGeorge, Ph.D., Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Robin Huff, Ph.D., HFD-570, Alternate Member  
Glenna Fitzgerald, Ph.D., Team Leader  
Ed Fisher, Ph.D., Presenting Reviewer

Author of Draft: Ed Fisher

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # —  
Drug Name: pregabalin  
Sponsor: Parke-Davis

#### Background:

Pregabalin is a GABA analogue being investigated for the treatment of epilepsy, pain, [ ] It is also chemically related to the approved antiepileptic gabapentin. It was negative in the genotox battery.

#### Mouse Study

Mice (64-66/sex/group) were given doses of 0, 200, 1000, or 5000 mg/kg in the diet for 2 years. The HD was expected to produce an AUC 25 times the human exposure at the maximum therapeutic dose (122 ug.hr/ml; 600 mg/day). The doses used were those recommended by the Division and CAC. A dose-related decrease in survival was seen at the MD and HD in both sexes. Overall survival percentages at Week 104 were 88, 80, 62, and 34% in males and 69, 68, 44, and 38% in females from the C, LD, MD, and HD groups, respectively. Statistically significant increases in BW were seen in males and females from all treatment groups compared to C (not D-R); at 104 weeks, the differences from C were 15, 21, and 15% in males and 19, 31, and 19% in females at the LD, MD, and HD, respectively. D-R increases in average food consumption were also seen in both sexes at all doses compared to C.

Incidences of hemangiosarcomas were dose-dependently increased in treated males and females, reaching statistical significance (Fisher's exact test) at the MD and HD in both sexes (3.1, 4.7, 29.2, and 34.4% in males and 3.1, 10.6, 29.7, and 38.5% in females from C, LD, MD, and HD groups, respectively; historical control range: 0-12% in males, 0-8% in females). These tumor findings correlated with clinical signs (palpable masses) and macroscopic findings (liver masses and enlarged spleens). Hemangiosarcomas occurred at multiple sites, but were most frequently found in the liver, spleen, and bone marrow. Hemangiosarcomas were considered the cause of death in 1, 3, 13, and 13 males and in 1, 3, 12, and 15 females in the C, LD, MD, and HD groups, respectively.

AUCs determined in a separate TK study using the same doses were 135, 800, and 3840 ug.h/ml in males and 148, 598, and 3740 ug.h/ml in females, respectively. Thus, mouse exposures at the LD, which were associated with increased incidences of hemangiosarcomas, are similar to exposures expected in humans.

#### Rat Study

Rats (65/sex/group) were given 0, 50, 150, and 450 mg/kg (males) or 0, 100, 300, and 900 mg/kg (females) in the diet for 2 years. They were based on the results of a 13-week rat study, with the HD considered an estimated MTD. The doses used were those recommended by the Division and CAC. Survival was increased in HD males and in females from all treatment groups at the end of the study. At

week 104, overall survival was 49, 45, 51, and 65% in males and 54, 74, 82, and 69% in females from the C, LD, MD, and HD groups, respectively. Overall BW gain was increased at the LD (13 and 30% in M and F, respectively), similar at the MD, and significantly decreased at the HD (22 and 41% in M and F, respectively), compared to C. BWs were significantly lower in HD males and females compared to C throughout the study (mean wts 13 and 24% below C at termination, in M and F, respectively). Food consumption followed the same pattern (8.9 and 13% below C in HDM and HDF, respectively, at 104 weeks).

There was no clear evidence of a T-R effect on the frequency of neoplasms in animals that died or were sacrificed moribund. Two rare tumors showed a positive trend: meningioma of the brain in males and squamous cell carcinoma of the skin in females. These were seen in 2 HD animals (3%) each and were not found in other groups. Historical control incidences of these tumor types in Wistar rats have been reported to range from 0-4%.

AUCs determined in a separate TK study using the same doses were 157, 600, and 1718 ug.h/ml in males and 306, 944, and 2930 ug.h/ml in females, respectively.

#### **Executive CAC Recommendations and Conclusions:**

The Committee concluded that both studies were adequate. They thought that the increased incidence of hemangiosarcomas in treated mice represented a true tumorigenic response to the drug. And they considered this finding to be of concern, since based on the present information, they could not say that it is not relevant to humans. Thus, they strongly disagreed with the following statement proposed by the sponsor for the pregabalin L

Furthermore, they did not consider the LD a no-effect dose for hemangiosarcomas, since the incidence in females mice was outside the historical control range at this dose.

The Committee suggested that if the sponsor believes that the tumor findings are specific to this strain, they could conduct a second 2-year bioassay in a different strain of mouse.

The Committee recommended that additional statistical analysis of the rat findings be conducted in which incidences of tumors histologically-related to the hemangiosarcomas found in mice be appropriately combined across tissues.

**Joseph DeGeorge, Ph.D.**  
Chair, Executive CAC

cc:\n  
/Division File, HFD-120  
/EFisher, HFD-120  
/GFitzgerald, HFD-120  
/JWare, HFD-120  
/ASeifried, HFD-024

/s/

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oseph DeGeorge  
2/21/00 04:49:51 PM

/s/

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ackie Ware  
2/29/00 02:10:16 PM  
igned for John S. Purvis

**Malandro, Lisa**

*Revised label*

**From:** Malandro, Lisa  
**Sent:** Friday, June 25, 2004 6:02 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Ware, Jacqueline H; Malandro, Lisa  
**Subject:** NDA 21-446 Pregabalin Label

*June 25, 2004*



June 25 PI final  
.doc (261 KB)...

Jonathan,

Attached is the Agency revised package insert for NDA 21-446. Please note that the language regarding abuse potential has been reinserted and will be retained until the dispute resolution is resolved.

The Division has one remaining request regarding the label:

In light of the PPAR data that you recently submitted, please write and insert a statement in the precaution section urging caution with co-administering pregabalin and a PPAR due to the combination having a higher likelihood of edema, weight gain and possibly CHF.

We anticipate resolving any remaining labeling issues during the teleconference scheduled for Wednesday, June 30 at 9:30 am.

Thanks!  
Lisa

27 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

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/s/

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Lisa Malandro  
7/6/04 04:36:31 PM

**Malandro, Lisa**

June 17, 2004  
Clinical IR

**From:** Malandro, Lisa  
**Sent:** Thursday, June 17, 2004 3:09 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Malandro, Lisa  
**Subject:** NDA 21-446 Pregabalin Information Request

Jonathan,

The following requests from the Division's clinical group are related to the ongoing review of the above pregabalin application. Please submit response to this request, as soon as possible, in electronic archival format as an amendment to NDA 21-446, NDA 21 723, NDA 21-724 [ 1

1. Among the patients in the controlled DPN trials, identify the subjects who took a peroxisome proliferator activated receptor (PPAR) medications such as troglitazone, rosiglitazone, or pioglitazone. Tabulate the number of patients in each dose group that were taking the respective PPARs.

Use these and the available AE data to compare the rates of :  
edema  
weight gain  
heart failure

in these patients to the rates in (1) DPN patients not taking a PPAR, and (2) the combined (all indications) population.

2. Perform similar analyses for the overall safety database as well.

Thank you,  
Lisa

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/s/

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Lisa Malandro  
6/18/04 11:27:23 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Robert J. Tannenber, M.D.  
East Carolina University Medical  
Brody 2N-72  
Greenville, North Carolina 27858

Food and Drug Administration  
Rockville MD 20857

JUN 15 2003

Dear Dr. Tannenber:

Between March 29 and 31, Mr. Perry H. Gambrell, representing the Food and Drug Administration (FDA), conducted an investigation to review the conduct of a clinical investigation (protocol # 1008-014 entitled: "A Double-Blind Placebo-Controlled Trial of Pregabalin for Treatment of Painful Diabetic Peripheral Neuropathy") of the investigational drug pregabalin (LYRICA), performed for Pfizer Global Research and Development. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Gambrell during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.  
Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

cc:  
T }

FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-170 Doc.Rm. NDA#21-446

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (Kashoki)

HFD-170 PM (Malandro)

HFD-46/47c/r/s/ GCP File # 11183

HFD-46/47 GCP Reviewer (Currier)

HFD-46/47 CS

HFR-SE150 DIB

HFR-SE150 Bimo Monitor (Hubbard)

HFR-SE1536 Field Investigator (Gambrell)

GCF-1 Seth Ray

r/d: Currier:5/14/04

reviewed:KMU:5/25/04

f/t:ml:6/1/04

[

]

**Reviewer Note to Rev. Div. M.O.**

This was a routine inspection assignment issued to verify the data for pending NDA 21-446, pregabalin (LYRICA). The inspection covered protocol 1008-014, site 012. Thirty-six subjects were screened and 18 completed the study. The inspection reviewed 7 of the 18 subject records in depth. No deficiencies were found. Three SAEs were reported to the IRB and sponsor: 1) macular edema – subject was dropped then let back into the study by the sponsor; 2) exacerbation of Crohne's disease – subject hospitalized and dropped from study; and 3) chest pain with hospitalization – subject remained in study.

Study data appear valid and could be used to support an approval decision for the NDA.

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/s/

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Khin U

6/18/04 09:15:01 AM

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** June 9, 2004  
**TO:** NDA 21-446 Study File  
**FROM:** Lisa Malandro  
**SUBJECT:** **Minutes of CMC teleconference**  
NDA 21-446, pregabalin

In a brief teleconference held on June 4, 2004, the following comments were relayed to the Sponsor by the Division's CMC review team. The Sponsor's responses are captured in italicized text.

1. We remind you of your commitment in the Amendment dated 13-MAY-2004 to test the first three Ringaskiddy lots of pregabalin for [ ] for which the [ ] process has been implemented. If the observed levels are more than [ ] PPM, submit the data in a prior-approval supplement and propose a specification of NMT [ ] PPM for this impurity.

*The Sponsor agrees to this commitment*

2. The batch reference for the [ ] was omitted for the manufacturing example in the NDA submission, Section 3.2.S.2.2.2 page 34. Adequately document the batch reference for the regulatory starting material in all future manufacturing campaigns.

*The Sponsor will evaluate this request and provide the Division with a response.*

3. The data in support of a [ ] retest interval for the drug substance were based on only three batches from Holland, MI. Statistical analysis revealed that at end of proposed retest interval, the tolerance limits were outside the acceptable range of [ ] Therefore, a retest interval of [ ] is granted at this time. Accrual of additional stability data may qualify for a future extension of the retest interval.

*The Sponsor agrees.*

4. Provide a revision to the drug substance specifications with the acceptance criteria for the bulk density of NLT  $\geq 2$  g/ml, which is reflective of the batch experience by the proposed process. This may be submitted in the next annual report.

*The Sponsor will evaluate this request and provide the Division with a response.*

5. A shelf life is granted only for the currently proposed configuration of the drug product, i.e. 60 cc HDPE bottles containing 60 capsules for the strengths 25-, 50-, 75-, and 100 mg.

*The Sponsor will evaluate this comment and may wish to discuss it at a later date via teleconference.*

6. For the strengths 150-, 200-, 225-, and 300 mg capsules, a shelf life of 24 months is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the shelf life may be extended in the next annual report.

*The Sponsor will evaluate this comment and may wish to discuss it at a later date via teleconference.*

7. Revise the post-approval stability protocol to 24 months.

*The Sponsor will evaluate this recommendation and provide the Division with a response.*

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

*The Sponsor agreed to address this recommendation.*

Additionally, the Sponsor agreed to re-evaluate their calculation of the head space in the capsules of higher strengths. The Division believes that this calculation is affecting the shelf-life.

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/s/

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Lisa Malandro  
6/16/04 05:40:41 PM  
CSO

Malandro, Lisa

CMC IR

June 8, 2004

From: Malandro, Lisa  
Sent: Tuesday, June 08, 2004 4:39 PM  
To: 'Parker, Jonathon M (Regulatory Affairs)'  
Cc: Ware, Jacqueline H; Malandro, Lisa  
Subject: NDA 21-446 Pregabalin CMC comments

Hi Jonathan,

Following are the CMC comments that were discussed during the teleconference on Friday, June 4, 2004.

List of CMC reminders and comments for resolution:

1. We remind you of your commitment in the Amendment dated 13-MAY-2004 to test the first three Ringaskiddy lots of pregabalin for [ ] for which the [ ] process has been implemented. If the observed levels are more than — PPM, submit the data in a prior-approval supplement and propose a specification of NMT — PPM for this impurity.
2. The batch reference for the [ ] was omitted for the manufacturing example in the NDA submission, Section 3.2.S.2.2.2 page 34. Adequately document the batch reference for the regulatory starting material in all future manufacturing campaigns.
3. The data in support of a [ ] retest interval for the drug substance were based on only three batches from Holland, MI. Statistical analysis revealed that at end of proposed retest interval, the tolerance limits were outside the acceptable range of [ ] Therefore, a retest interval of [ ] is granted at this time. Accrual of additional stability data may qualify for a future extension of the retest interval.
4. Provide a revision to the drug substance specifications with the acceptance criteria for the bulk density of NLT ~ g/ml, which is reflective of the batch experience by the proposed ~ process. This may be submitted in the next annual report.
5. A [ ] shelf life is granted only for the currently proposed configuration of the drug product, i.e. 60 cc HDPE bottles containing 60 capsules for the strengths 25-, 50-, 75-, and 100 mg.
6. For the strengths 150-, 200-, 225-, and 300 mg capsules, a shelf life of [ ] is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the shelf life may be extended in the next annual report.
7. Revise the post-approval stability protocol to include semi-annual testing in the first and second year of testing.
8. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, your continued cooperation is expected to resolve any problems that may be identified.

Please submit response to these requests in electronic archival format as amendments to NDA 21-446, NDA 21-723, NDA 21-724, [ ]

Thank you,

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/s/

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Lisa Malandro  
6/8/04 04:39:21 PM

Preapproval Safety Mtg  
March 22, 2004

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** June 1, 2004

**TO:** NDA 21-446 Study File

**FROM:** Lisa Malandro

**SUBJECT:** **Minutes of Action Briefing/Preapproval Safety Conference**  
NDA 21-446, Lyrica (pregabalin) Capsules

A preapproval safety conference was held on March 22, 2004, in order for reviewers, team leaders, and other Division personnel to discuss the safety issues associated with NDA 21-446 pregabalin indicated for the treatment of neuropathic pain associated with diabetic polyneuropathy. Previous to this meeting, on March 19, 2004, a Regulatory Briefing meeting was also held to discuss some of these safety issues. Each discipline gave an overview of outstanding issues as well as safety concerns, as follows:

**CMC** – At the time of this meeting, the CMC staff had one outstanding safety issue regarding the level of  $C_{max}$  and whether or not this compound is a known carcinogen. If  $C_{max}$  is a known carcinogen, the Sponsor will have to commit to limiting the amount of the compound found in the drug product. (Post meeting note: This issue was addressed with the Sponsor during a teleconference). The CMC staff also stated that they had a few comments for the Sponsor regarding their comparability protocol. These comments can be addressed by the Sponsor in the form of a post-approval supplement. The CMC staff stated that they have no further approveability issues at this time.

**Pharm/Tox** – In addition to the hemangiosarcoma/hemangioma issues discussed at the Regulatory Briefing, the Pharm/Tox staff presented concerns regarding the teratogenicity of pregabalin. The Pharm/Tox staff feels that this is not an unusual finding in anti-convulsant drugs. They stated that there is a safety margin, but that there appears to be a profound effect on male fertility including decreases in sperm motility and fertility. The Pharm/Tox staff concluded that this issue would be addressed in the product label.

**Biopharm** – The Biopharmaceutics staff indicated that pregabalin does not inhibit any other drugs. They stated that the dose of pregabalin should be adjusted for renal function and the elderly. The Biopharm staff suggested that pregabalin may induce the metabolism of other drugs and stated that this should be followed-up as part of a Phase 4 study. The Biopharm staff also stated that there was inadequate data to evaluate whether or not there was a QTc deficiency and suggested that this also be followed-up as a Phase 4 study. At the time of the meeting, the

Biopharmaceutics staff had one outstanding issue related to the dosing regimen; **1** however, their data supports dosing TID.

**Clinical** – In addition to the safety concerns described during the Regulatory Briefing, the Clinical Staff will request a Phase 4 study in order to better evaluate the apparent decreases in visual acuity and the visual field deficits. During the Regulatory Briefing, an attendee suggested that the Division consider issuing a Medication Guide in order to address this safety concern. The Clinical Staff is currently evaluating the possibility that pregabalin causes elevated creatine kinase levels which may lead to rhabdomyolysis.

**CSS** – The CSS staff has recommended to the DEA that pregabalin be controlled under the Controlled Substances Act as a Class IV drug. The CSS staff explained that, until the scheduling process is completed by the DEA, the Sponsor will be unable to market this drug. The recommendation for scheduling was based upon findings of euphoria in patients being treated for anxiety (10-12%), a similarity in abuse potential by known drug abusers classifying pregabalin as being as “likeable” as benzodiazepines, and evidence of self-administration in monkeys. It was decided that a Discipline Review letter should be prepared and sent to the Sponsor so that they are aware of this issue.

**/S/**

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Lisa Malandro  
Regulatory Project Manager

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/s/

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Lisa Malandro  
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2 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

## Office of Drug Safety

# Memo

**To:** Russell Katz  
Director, Division of Neuropharmacological Drug Products, HFD-120

**From:** Alina R. Mahmud, R.Ph.  
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety  
HFD-420

**Through:** Carol Holquist, R.Ph.  
Director, Division of Medication Errors and Technical Support, Office of Drug Safety  
HFD-420

**CC:** Lisa Malandro  
Project Manager, HFD-120

**Date:** May 18, 2004

**Re:** ODS Consult 03-0282-1; Lyrica (Pregabalin Capsules); NDA 21-446.

---

This memorandum is in response to a May 4, 2004, request from your Division for a re-review of the proprietary name, Lyrica.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Lyrica since we conducted our review dated on February 3, 2004 (ODS consult 03-0282) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

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Alina Mahmud  
5/20/04 11:09:41 AM  
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-446  
NDA 21-723  
NDA21-724

Type A  
Abuse Liability  
Meeting Minutes  
5-17-04

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS  
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to the meeting between representatives of your firm and FDA on April 13, 2004. The purpose of the meeting was to discuss the preliminary assessment by the Controlled Substance Staff (CSS) that pregabalin be considered for Scheduling under the Controlled Substances Act.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7416.

Sincerely,

*{See appended electronic signature page}*

Lisa Marie Malandro  
Regulatory Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## Industry Meeting Minutes

**Date/Time:** June 26, 2003 / 1:30 pm      **Location:** Parklawn, Conference Room 17-05

**Application:** IND 53,763

**Sponsor:** Pfizer

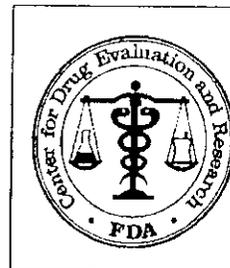
**Drug/Dosage Form:** Pregabalin (CI-1008)/Capsules

**Indication:** Neuropathic pain

**Type of Meeting:** Type A

**Meeting Chair:** Sharon Hertz, M.D., Team Leader, Analgesics

**Minutes Recorder:** Lisa M. Malandro, Regulatory Project Manager



<b>Sponsor Attendees</b>	<b>Title</b>
R. Michael Poole, M.D.	Clinical Development
Lloyd Knapp, Pharm.D.	Clinical Development
Jonathon M. Parker, R.Ph., M.S.	Regulatory Affairs
( )	Consultant
( )	Consultant
Cheryl Graham, M.D.	Regulatory Affairs
<b>FDA Attendees</b>	<b>Title</b>
Bob Rappaport, M.D.	Acting Director
Sharon Hertz, M.D.	Team Leader, Analgesics
D. Elizabeth McNeil, M.D.	Clinical Reviewer
Lisa M. Malandro	Regulatory Project Manager
Jonathan Roberts	Pharmacy Student Intern

**Meeting Objective(s):** To seek the Division's agreement that Pfizer has addressed the issue that efficacy for pregabalin is not attributable to nerve damage in diabetic peripheral neuropathy (DPN) patients and to discuss the need, if any, for an additional clinical study.

**General Discussion:** Following introductions, the discussion focused on the sponsor's questions that were included in the April 18, 2003, meeting package. The sponsor's questions are presented below in bolded text. Agency responses, prepared prior to the meeting and presented on slides, are italicized. Discussion is presented in normal text.

**Question 1: After reviewing the data package submitted on April 18, 2003 (Serial 0335), does the Division have sufficient information on this issue to determine that the data to be included in the pregabalin NDA for the management of neuropathic pain associated with DPN will allow for filing?**

**FDA RESPONSE**

- You have enough information on this issue to submit an application.*
- A file/refuse to file decision would be made within 60 days of submission receipt.*

**Question 2: Does the Division agree that these data are consistent with the conclusion that the efficacy of pregabalin in DPN patients is not attributable to acceleration of nerve damage?**

**FDA RESPONSE**

- We do not yet have sufficient data to make the definite conclusion that pregabalin does not cause nerve damage.*

**Question 3: Based on the data that we will be providing in the pregabalin NDA (pharmacology, toxicology, clinical data including neuropathy scores and return of pain after withdrawal from pregabalin), will sufficient information be available during the review to conclude that efficacy of pregabalin is not attributable to accelerated nerve damage?**

**FDA RESPONSE**

- You must submit one AWC study demonstrating that efficacy does not correlate with accelerated nerve damage, using a quantitative measure of nerve function*
- At the time of NDA submission, please submit complete CRFs for the 106 patients who experienced drug holidays.*

**DISCUSSION**

Dr. McNeil stated that the meeting package proposed a 2-week study to determine whether there was any pregabalin associated nerve toxicity, and clarified that a 12-week study including nerve function tests was necessary. Dr. Hertz noted that the original studies completed for this indication were not designed to address the issue of potential nerve toxicity. She stated that the drug holiday portion of the open-label data is supportive of a lack of toxicity, but not definitive.

Dr. Hertz stated that, based on previous discussions and the nonclinical data, and the supportive open-label data, it will be acceptable for the Sponsor to complete this study as a Phase 4 commitment. Dr. Hertz clarified that this situation is specific to the current application for pregabalin. Future applications for products designed for use in the treatment of neuropathic pain would require at least one adequate, well-controlled clinical study including nerve conduction velocity tests prior to submission of the NDA.

The Sponsor questioned the Division's rationale for preferring a 12-week study. Dr. Hertz stated that the Division feels that it is important to collect electrophysiological data during the same time frame that proof of efficacy data are being collected. The Sponsor questioned whether the Division would accept a 6-week study. Dr. Hertz stated that only profound injuries would be detectable within a 6-week time frame. Since the physiology and mechanism of action for pregabalin are unknown, it would be difficult to determine if symptom relief was due to slowly developing nerve toxicity or due to a therapeutic effect of pregabalin administration. The Sponsor agreed to commit to the Phase 4 study and plans on submitting a protocol for the Division to review by the end of July, 2003.

Dr. Hertz inquired about the Sponsor's progress towards addressing the clinical hold. The Sponsor stated that the remaining data will be submitted to the Agency in two parts. The second mouse carcinogenicity study will be submitted in July, 2003. The additional toxicology information will be submitted in September, 2003. The Sponsor suggested that a meeting be held with the Division of Neuropharmacology Drug Products (HFD-120) in order to coordinate the timing and reduce the review burden on the two Divisions. Dr. Rappaport suggested that the Sponsor submit a proposal and a teleconference be scheduled in order to address the timing and review issues.

Dr. Hertz questioned who would be considered potential recruits for the previously discussed clinical study under the conditions of the current clinical hold. She expressed concern that patients who are non-responders to gabapentin would also be non-responders to pregabalin. The Sponsor stated that the inclusion criteria for the study will be important and that, under the current clinical hold, only a highly refractory population that would not provide appropriate data would be available. The Sponsor stated that they would focus on completing administrative tasks and would not begin the clinical study until the clinical hold was lifted.

Dr. Rappaport stated that he understands that nerve conduction velocity studies are not ideal requirements for proving that a drug being developed for the treatment of neuropathic pain is safe and effective. Further, he stated that the Division often struggles with alternative study designs. Dr. Rappaport requested that the consultants, [redacted] J, provide the Division with their opinions of current requirements and alternative options.

Dr. [redacted] stated that if efficacy is defined as pain relief, then nerve damage often causes the opposite effect. Therefore, pain improvement would not be explained by nerve toxicity. Often, neurotoxicity is evident by Week 2 of a study. If an axon is transected, a signal is recordable for 7 to 10 days. Dr. [redacted] stated that in a 6-week study (2-weeks of treatment and a 4-week follow up) standard electrophysiology tests such as measures of amplitude are the best since the amplitude is equal to the number of functioning axons.

June 26, 2003

Dr. — stated that changes in pain and nociceptors can be part of a process causing changes in axons. He said that 6-week studies are adequate, but that 12-week studies are also reasonable. Dr. — confirmed that electrophysiology measures provide highly objective and highly effective data. He stated that the Division's current program is reasonable. Dr. — asked what was considered a reasonable change in magnitude (1.5 meters/second). Dr. Hertz stated that she agreed that amplitude may provided more relevant data reflecting loss of axons as the nerve fibers that are involved in the symptoms of pain in diabetic neuropathy are normally slow and contribute a limited amount to the overall conduction velocity. In order to assess nerve function, the Division would like to see the results of studies of multiple nerves with amplitude and velocity.

The meeting adjourned at 2:30 pm

Minutes prepared by:

Lisa M. Malandro

*{See appended electronic signature page}*

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/s/

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Lisa Malandro  
7/23/03 03:01:53 PM

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** June 3, 2004

**TO:** Bob Rappaport, M.D., Director  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

**VIA:** Lisa Malandro, Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M. D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** ODS/DSRCS Review of Medication Guide for Lyrica (pregabalin)  
Capsules Capsules, NDA 21-446

### Summary

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling (Medication Guide) Lyrica (pregabalin) Capsules, NDA 21-446. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling dated March 15, 2004 and revised by the review division. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the MG.

The Patient Information Subcommittee (PISC) recommended a MG for pregabalin (April 12, 2004) because of the serious and significant public health concern of vision changes associated

with the product.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

Malandro, Lisa

CMC IR

5-14-04

From: Jani, Parinda  
Sent: Friday, May 14, 2004 11:24 AM  
To: 'jon.parker@pfizer.com'  
Cc: Malandro, Lisa  
Subject: Additional CMC comments

Hi Jonathan:

Did you get my email from yesterday? Following are additional CMC comments. Let me know if you have any questions.

1. It is not clear from the NDA if [ ] was employed in the production of the drug substance lots that were monitored and were found to contain levels below the LOQ of [ ]. Also, there is no specification for [ ] in the [ ] that are likely used in the same or earlier step in the manufacturing process. Therefore provide assurance that the drug substance will be monitored for the presence of [ ] if the [ ] and if [ ] are used during the manufacture.
2. During a teleconference on April 8, 2004 among the review division, the field office and your firm, it was agreed that a revised specific ID test will be proposed to distinguish between pregabalin and gabapentin and that a hierarchical testing approach will be proposed to proceed with the testing of the test attributes only after the specific ID test is carried out. Therefore, provide the updated ID specification, method and validation summary.
3. During a teleconference on April 23, 2004 you agreed to provide analytical data on the [ ] [ ] levels in the drug substance batches used in the clinical studies and to establish a specification of NMT - PPM for this carcinogenic impurity in the drug substance by not later than the second week of May 2004. Therefore, provide this data to the NDA at an earliest.
4. Provide the following additional criteria in the comparability protocol for the [ ] route to pregabalin.
  - (a) Clear description of the change controls for the [ ] for the starting material [ ]
  - (b) A clear statement that the analytical method(s) for the assay and impurities of the starting material, [ ] shall be sensitive and discriminatory enough to detect and quantify the process impurities from [ ] that may possibly be used by the vendors.
  - (c) A clear statement that the maximum levels of the non-structural alert impurities [ ] will not exceed 0.1% individually in the drug substance.
  - (d) A statement that the drug substance purity shall be assessed by the [ ] HPLC methods used to quantify the impurities [ ] in the assay of the drug substance manufactured by the [ ] of synthesis.

- (e) A statement that the protocol shall not be modified without the Agency concurrence in the event of a failure,
- (f) Provide the following additional specifications for the carcinogenic impurity  $\text{C}$  and the structural alert impurities in the drug substance:

$\left. \begin{array}{l} \text{NMT} - \text{PPM} \\ (\text{PD} \cdot \text{C}) : \text{NMT} - \text{PPM} \\ (\text{PD} \text{ C}) : \text{NMT} - \text{PPM} \\ (\text{PD} \text{ C}) : \text{NMT} - \text{PPM} \end{array} \right\}$

- (g) Provide the following additional specifications for the drug substance:

$\left. \begin{array}{l} \text{NMT} - \% \\ : \text{NMT} - \text{PPM and reflective of the actual observed data} \\ \text{NMT} - \text{PPM} \end{array} \right\}$

Thanks

Parinda Jani  
 Chief, Project Management Staff  
 Division of Anesthetic, Critical Care and  
 Addiction Drug Products  
 Office of Drug Evaluation II  
 Center for Drug Evaluation and Research  
 Tel # (301) 827-7422  
 Fax # (301) 443-7068

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/s/

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Lisa Malandro  
5/19/04 05:25:19 PM

Malandro, Lisa

CMC IR

From: Jani, Parinda  
Sent: Thursday, May 13, 2004 4:42 PM  
To: 'jon.parker@pfizer.com'  
Cc: Malandro, Lisa  
Subject: FW: NDA 21446 Comment to Sponsor

5-13-04

Hi Jonathan:

These are the comments from the CMC reviewer. My understanding is that some additional comments for the "comparability protocol" will be forthcoming, hopefully, early next week. Call me if you have any questions.

Parinda

Provide a full description of the container/closure system for the 60 cc HDPE bottle in section 3.2.P.7 of the NDA.

Provide a letter of Authorization to reference the DMF for the 1 HDPE bottle.

Provide a commitment to place the 1 HDPE bottles on stability or justify why this is not needed based on the bracketing considerations in the existing stability protocol.

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/s/

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Lisa Malandro  
5/19/04 05:19:00 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-446  
NDA 21-723

NDA 21-724

Type A meeting req.  
Denied

5-10-04

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS  
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA (pregabalin) Capsules, 20/50/75/100/150/200/225/300 mg.

We also refer to your May 3, 2004, correspondence, received May 4, 2004, requesting a Type A meeting to discuss the interpretation of the available ophthalmologic data. We have considered your request and concluded that the meeting is unnecessary. Discussions pertaining to the Division's labeling revisions will be completed as part of standard labeling communications.

If you have any questions, call me at (301) 827-7416.

Sincerely,

*{See appended electronic signature page}*

Lisa Malandro  
Regulatory Health Project Manager  
Division of Anesthetic, Critical Care  
And Addiction Drug Products, HFD-170  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Lisa Malandro  
5/10/04 02:33:34 PM

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

*Type A Abuse Liability  
Meeting Confirmed*

**DATE:** April 27, 2004  
**TO:** NDA 21-446, 21-723, 21-724C  
**FROM:** Lisa Malandro  
**SUBJECT:** Meeting request dated April 9, 2004  
LYRICA™ (pregabalin) Capsules,  
20/50/75/100/150/200/225/300 mg

J Study Files 4-27-04

A meeting request for a Type A meeting was received by each of the above referenced new drug applications on April 12, 2004, in order to discuss the preliminary assessment by the Controlled Substances Staff that pregabalin be considered for scheduling under the Controlled Substances Act. Due to the priority review status of NDA 21-446 the meeting was scheduled through communications with the Sponsor prior to receipt of the meeting request. The meeting was held on April 13, 2004. No formal letter granting the meeting was generated since the meeting occurred at the same time as receipt of the meeting request by the Division. This memo serves to document that the meeting was granted by the Controlled Substances Staff and the Division of Anesthetic, Critical Care and Addiction Drug Products.

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/s/

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Lisa Malandro  
4/27/04 11:11:20 AM

TC u: C  
April 23, 2004

J

### MEMORANDUM OF TELECONFERENCE

DATE: April 23, 2004

APPLICATION NUMBER: NDA 21-446, Lyrica (pregabalin) Capsules

BETWEEN:

Name: Representatives of Pfizer Inc.,

AND

Name: Lisa Malandro, Regulatory Project Manager  
Eric Duffy, Ph.D., Director, Office of New Drug Chemistry II  
Dan Mellon, Ph.D., Supervisory Pharmacologist  
Ravi Harapanhalli, Ph.D., Supervisory Chemist  
Jerry Cott, Ph.D., Pharmacologist  
Sharon Kelly, Ph.D., Chemist  
Division of Anesthetic, Critical Care, and Addiction Drug Products,  
HFD-170

SUBJECT: Presence of [ ]

A teleconference was held on April 23, 2004, between representatives of Pfizer, Inc. and the above listed Division representatives in order to discuss the possibility that [ ] exist in the pregabalin drug product. Dr. Mellon explained to the Sponsor that the Agency is asking Sponsors to evaluate drug products to see if these types [ ] exist. Dr. Mellon stated that there is a potential for [ ] to be present in pregabalin. The Sponsor stated that theoretically the [ ] could exist, but that they believe it is [ ] used during the manufacturing process. Dr. Harapanhalli stated that the rationale that the Sponsor provided the Division was speculative in nature and that the Sponsor should limit the presence [ ] to [ ] ppm based upon the current government standard (ICH QC3). The Sponsor stated that they are using a very sensitive [ ] test to determine if the [ ] is present and that the data would be submitted during the week of May 3 or 10, 2004. The Sponsor also agreed to provide a rationale stating why they believe that the [ ] will not develop over time.

|S|

\_\_\_\_\_  
Lisa Malandro  
Regulatory Project Manager

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/s/

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Lisa Malandro  
6/1/04 04:58:35 PM  
CSO

**Malandro, Lisa**

Pharm Tox IR

4/22/04

**From:** Malandro, Lisa  
**Sent:** Thursday, April 22, 2004 10:25 AM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Malandro, Lisa; Ware, Jacqueline H  
**Subject:** NDA 21-446, -723, -724 PharmTox Request  
**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Jonathan,

I received the following request from the Pharmacology/Toxicology staff. Please submit a response to this request electronically as an amendment to each NDA.

The Pharmacology Reviewer noted that the positive controls used in 4 genetic toxicology studies submitted in support of the Pregabalin NDA for Diabetic Neuropathic pain may not meet the current standards. Specifically, the OECD (and EPA and CFSAN) Protocols indicate the following:

"OECD Guidelines state: 2-Aminoanthracene should not be used as the sole indicator of the efficacy of the S9-mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g., benzo(a)pyrene, dimethylbenzanthracene." Four in vitro mutagenicity studies with pregabalin used 2-aminoanthracene as the sole agent without specifying how the activity of each batch was characterized."

Our request is this: Provide evidence that the S9 used in the the following genetic toxicology studies was characterized with a mutagen that requires metabolic activation by microsomal enzymes (i.e., benzo (a)pyrene or other). The four study numbers that appear to only use only 2-aminoanthracene are as follows: 745-03418, 745-02035, 745-03320, and 745-03203.

If you have any questions, please do not hesitate to contact me.  
Thanks, Lisa

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/s/

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Lisa Malandro  
7/9/04 04:24:17 PM

**Malandro, Lisa**

CMC IR

4-19-04

**From:** Malandro, Lisa  
**Sent:** Monday, April 19, 2004 1:29 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Pregabalin

Jonathan,

Following is a request from the Chemistry and Pharmacology reviewers.

We have reviewed your 17 February 2004 submission to NDA 21-446 sent in response to the Agency's question as follows:

**Question:** Provide data on the observed levels of [ ] in the drug substance batches used for the production of the drug product batches that were used in the pivotal and primary stability studies.

**Response:** There is not drug substance data available for [ ] since the expectation is that this impurity would not be observed in pregabalin API lots.

Your response and justification regarding the carcinogenic impurity [ ] is inadequate. Our internal discussion within the CMC and Pharm/Tox disciplines and with the CardioRenal Division points out that a specification of NMT ~~—~~ PPM be established for this impurity. The CMC Reviewers and PharmTox Reviewers of NDA 21-446 are available for a teleconference to further discuss the issue.

We'll talk to set-up a teleconference time.  
Lisa

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/s/

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Lisa Malandro  
4/20/04 01:00:36 PM

**Malandro, Lisa**

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**From:** Malandro, Lisa  
**Sent:** Monday, April 19, 2004 1:24 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** FW: NDA 21-446 Pregabalin  
  
**Importance:** High  
  
**Contacts:** Jonathon M Parker (Regulatory Affairs)

*Draft Labeling  
sent to Sponsor  
for MedGuide  
Preparation*

*4-19-04*

-----Original Message-----

**From:** Malandro, Lisa  
**Sent:** Monday, April 19, 2004 12:32 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Pregabalin  
**Importance:** High

Hi Jonathan,

Attached in a Word document is the Division's draft of the Warnings/Precautions sections of the label for pregabalin. Please use this as a guideline for preparing the MedGuide. If you have any questions, please contact me.

Thanks,  
Lisa



WARNING  
:cautions.doc (54 KE)

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§ 552(b)(5) Draft Labeling

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/s/

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Lisa Malandro  
4/20/04 12:54:44 PM  
CSO

**MEMORANDUM OF MEETING MINUTES**



**Meeting Date:** March 19, 2004      **Time:** 1:00-3:00 PM

**Location:** Rockwall, Conference Room 1033

**Application:** NDA 21-446 LYRICA (pregabalin) Capsules

**Indication:** Treatment of neuropathic pain associated with diabetic peripheral neuropathy

**Meeting:** Regulatory Briefing

**Presentation:** Bob Rappaport, M.D., Division Director, HFD-170  
 Mwango Kashoki, MD, MPH, Clinical Reviewer, HFD-170  
 Jerry Cott, Ph.D., Pharmacology/Toxicology Reviewer, HFD-170

**Meeting Chair:** Steven Galson, MD, MPH, Acting Director, CDER

**Meeting Recorder:** Lisa Malandro, Project Manager, HFD-170

**FDA Attendees, Titles, and Office/Division:**

<b>Attendee</b>	<b>Title, Office/Division</b>
Steven Galson, M.D., M.P.H.	Acting Director, CDER
John Jenkins, M.D.	Director, Office of New Drugs
Bob Temple, M.D.	Associate Director for Medical Policy, OMP Acting Director, ODE I
Edward Cox, M.D.	Deputy Director, ODE IV
John Alexander, M.D., MPH	Medical Team Leader, DAIDP
Abigail Jacobs, Ph.D.,	Associate Director for Pharm/Tox, ODEs 4 and 5, HFD-024
Solomon Sobel, M.D.	Associate Director for Medical Affairs, OPS, HFD-003
Bob Rappaport, M.D.	Director, DACCADP, HFD-170
Rigoberto Roca, M.D.	Deputy Director, DACCADP, HFD-170
Celia Winchell, M.D.	Team Leader, Addiction Drugs, DACCADP, HFD-170
Daniel Mellon, Ph.D.	Pharmacology/Toxicology Team Leader, DACCADP, HFD-170
Mwango Kashoki, M.D., M.P.H.	Medical Officer, DACCADP, HFD-170
Jerry Cott, Ph.D.	Pharmacology/Toxicology Reviewer, DACCADP, HFD-170
Lisa Malandro	Regulatory Project Manager, DACCADP, HFD-170

Russell Katz, M.D.	Director, DNDP, HFD-120
Judy Racoosin, M.D	Safety Team Leader, DNDP, HFD-120
Alice Hughes, M.D.	Safety Reviewer, DNDP, HFD-120
Jerry Boehm, M.D.	Safety Reviewer, DNDP, HFD-120
Lois Freed, Ph.D.	Pharmacology/Toxicology Team Leader, DNDP, HFD-120
Ed Fisher, Ph.D.	Pharmacology/Toxicology Reviewer, DNDP, HFD-120
Ken Hastings, Ph.D.	HFD-024
Terry Peters, DVM	Pharmacologist, HFD-520
Wiley Chambers, M.D.	Deputy Director, HFD-550
Terry Martin	Regulatory Health Project Manager, HFD-006
Deborah Leiderman, M.D.	Director, CSS, HFD-009
Ed Cox	Supervisory Medical Officer, HFD-104
Mark Goldberger	Supervisory Medical Officer, HFD-104
Roswitha Kelly	Math Statistician, HFD-710

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### OPENING REMARKS:

Following opening statements by Ms. Terry Martin, Dr. Bob Rappaport began the meeting by giving an overview of the history of neuropathic pain drugs within the Agency prior to their being assigned to the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170). Following the transfer, the Division held an Advisory Committee Meeting, re-evaluated the requirements for drugs of this type and is drafting guidance for industry in order to assist with their development plans. Dr. Rappaport stated that the New Drug Application (NDA) that the Division would discuss today is under "priority" review for the symptomatic treatment of diabetic peripheral neuropathy (DPN). Concurrently, LYRICA is under "standard" review for neuropathic pain associated with post-herpetic neuralgia (PHN),  $\xi$

Dr. Rappaport explained that the pain of DPN is a severe disorder for which there is no approved treatment and, therefore, a priority review is warranted.

### BACKGROUND:

Drs. Kashoki and Cott presented the results of the efficacy review, the history of Lyrica (pregabalin) in the Agency and the issues causing safety concerns.

Briefly, the safety concerns include:

1. The preclinical data show that pregabalin is carcinogenic in mice. The Sponsor states that this is a species-specific finding but, despite extensive testing, has not been able to conclusively demonstrate this assertion.
2. The dermatopathy seen in animals creates concern that pregabalin could contribute to skin breakdown in humans (particularly patients with diabetes), although no clinical correlation has been demonstrated in the available data.
3. The clinical data show an effect of pregabalin on visual acuity based on adverse event reports. However, the visual effects of the drug have not been well-characterized due to inadequacies of the formal testing included in the development program.

Together, the possibility of drug-related effects on skin integrity and the poorly characterized effects of pregabalin on visual parameters represent a concerning level of risk in the diabetic population, which is at particular risk of morbidity related to both of these effects. Furthermore, since the product is renally cleared, this population may be at increased risk of developing drug-related adverse events because of underlying diabetes-induced renal impairment.

Detailed information about these issues can be found in **Attachments A** (Background Information) and **B** (Regulatory Briefing Presentation).

### QUESTIONS & DISCUSSION:

*Question 1: The Division believes that the relevance of the preclinical carcinogenic findings to humans cannot be ruled out and that the risk of drug-associated cancer should be included in the labeling. Does the Panel agree?*

The panel agreed that the apparent risk of drug-associated cancer is not sufficient to preclude approval of this drug since the DPN patient population is in need of effective medication and, therefore, this

concern should be addressed in the drug label. Drs. Galson and Jenkins suggested that the Division evaluate the data to determine if there is a subset of patients who are more probable responders to pregabalin. Limitation of the drug to a subset of probable responders or to a subset of patients with moderate-to-severe neuropathy may be considered if supported by the data and if the drug is approved. Dr. Temple suggested that, since the 300-mg and 600-mg doses have similar efficacy results, the Division should consider limiting the dose to 300 mg, with a starting dose of 150 mg if the adverse events are dose-related.

*Question 2: The Division proposes that the dermatologic and ophthalmologic effects of pregabalin should be better characterized prior to drug approval in order to establish that the risk/benefit ratio is favorable in the diabetic population. Does the panel agree?*

The following discussion pertains to the **dermatologic** findings and concerns:

Dr. Jenkins stated that the Division's concerns are based on animal findings, but that there is a large human database that did not show any increase in dermatologic findings. The panel discussed the length of the exposure in animals in comparison to that in the human clinical trials. The panel was asked for suggestions of other studies that the Division could request from the Sponsor to evaluate the dermatological changes. Dr. Hastings stated that the monkey study completed in 1995 could be repeated in order to better characterize the lesion, however, even if such information is available, it would be a labeling issue, not an "approvability" issue. Dr. Racoosin suggested that the Division (or Sponsor) evaluate the dose-related open label clinical study data to aggregate the amount of time each person was on each dose and determine the exposure. Dr. Jenkins stated that the data are confounded by the patients' underlying disease and he cannot think of anything else the Division could request to help characterize this. Dr. Racoosin suggested ☐

☑ Dr. Terry Peters stated that vasculopathy was only seen in the 4-week i.v. monkey study, and that she did not see these findings when she reviewed two, two-year rodent studies or two repeated-dose monkey studies. An attendee stated that, in the event that pregabalin does cause a 5-10% risk of increased ulceration, some patients would choose this risk in an effort to relieve their pain i.e., the risk would be outweighed by the benefit.

The panel recommended that the dermatologic findings were not an approvability issue. They suggested that the Division consider ☐

☑ was an appropriate way to continue to evaluate this issue.

The following discussion pertains to the **visual acuity and visual field deficit** findings and concerns:

Dr. Chambers stated that the application included formal testing conducted in such a way that it was not sensitive to minor changes, rendering the evaluation the equivalent of a "large, simple trial." Nevertheless, a treatment effect was detected despite the insensitivity of the measures. There was no pattern to the findings. Dr. Chambers stated that, in his opinion, this was also a labeling issue. He also stated that the application lacks sufficient information regarding the effect of pregabalin on vision, and a post-marketing study (100-200 patients/group, dosing for 8-12

weeks in duration followed by a wash-out phase ) to better define the mechanism of action in the ocular system and including threshold testing would be appropriate. Further, Dr. Chambers stated that the results of such a post-marketing study would not be confounded by the effects of diabetes on the eye since the symptoms are very different. Dr. Chambers explained that it would be difficult to collect these data prior to drug approval since the changes are not occurring very quickly. In the data that he evaluated, no one was approaching blindness. The studies did not include good baselines or quantitative data. The open-label data is difficult to evaluate; however, there were no severe visual losses.

Dr. Temple stated that the risk of visual acuity and visual field deficit seems tolerable for this patient population with appropriate labeling and a Phase 4 commitment.

#### **OTHER DISCUSSION POINTS:**

1. **Abuse Liability.** The Controlled Substance Staff (CSS) has recommended that the DEA schedule pregabalin as Schedule 4. Dr. Leiderman stated that in the clinical studies an increase in "euphoria" was evident. The incidence was detected in all indications although highest in the GAD population. "Euphoria" was not noted in the clinical study reports in the gabapentin NDA. Dr. Leiderman explained that the scheduling process occurs simultaneously with the review process. The Sponsor has signed an understanding that they cannot market the drug until the scheduling process is completed. A comment regarding the scheduling would go into an action letter. Since the scheduling process could take up to a year, it may affect the Sponsor's ability to market, even though the time period protected by Hatch-Waxman exclusivity would have begun.
2. **Increases in creatinine kinase (CK).** Dr. Racoosin stated that there is evidence that pregabalin appears to increase mean CK values in any of the ~~the~~ indications. There is one unconfounded case of rhabdomyolysis. The Divisions (HFD-170 and HFD-120) have requested additional data from the Sponsor.
3. **Current Treatment.** Dr. Rappaport explained that Neurontin is frequently prescribed and is efficacious for some DPN patients, but is not approved for that indication. □

□ Dr. Rappaport said that opiates are approved for "pain," prescribed for DPN, and sometimes effective in the treatment of neuropathic pain. It would, therefore, be possible to limit the use of pregabalin to "patients who have failed analgesic therapy."

4. **MedGuide.** Dr. Temple suggested that a MedGuide may be appropriate for pregabalin.

#### **SUMMARY OF RECOMMENDATIONS:**

1. Overall recommendation: Based upon the efficacy of pregabalin, the seriousness of the disease, and lack of treatment options, the Division should consider approving the drug for a limited population with appropriate labeling to address the safety concerns and Phase 4 commitments to monitor these concerns.

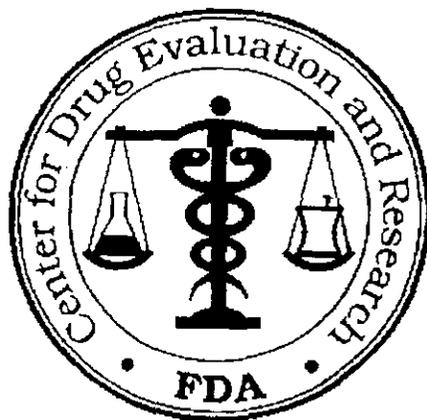
2. Recommended Phase 4 commitments:
  - a) Study a cohort of patients over time with a focus on defining the visual acuity and visual field effects.
  - b)  .
3. Recommended additions to the label:
  - a) Regular ophthalmological examinations and discontinuation of pregabalin if changes in visual acuity and/or visual field effects are recommended
  - b) Limitation of patient population to those experiencing “moderate to severe pain”
  - c) Limitation of patient population to those “failing alternative analgesic therapy”
  - d) Limitation of the dose to begin at 150 mg, not to exceed 300 mg
  - e) Risk of cancer; due to hemangiomas/hemangiosarcomas observed in mice
  - f) Risk of skin changes; due to the increased risk of dermatopathy seen in animal studies
4. Recommended analyses:
  - a) Analyze a subset of responders with duration of pain and symptoms as a variable
  - b) Determine if there is a subpopulation of responders
5. Remaining issues:
  - a) Evaluation of CK data and risk of rhabdomyolysis
  - b) Drug scheduling due to abuse liability
  - c) Preparation of a MedGuide to address the visual acuity and visual field effects

**Attachment A**  
**Background Information**

**Regulatory briefing for Pregabalin (LYRICA™)**

**NDA 21-446:  
Treatment of Diabetic Peripheral Neuropathy**

**March 19, 2004**



Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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**Background: Diabetic peripheral neuropathy (DPN)**

Diabetes mellitus is a disease of abnormal glucose metabolism. There are several complications of diabetes of long duration and/or poor glycemic control, including nephropathy, retinopathy, peripheral vascular insufficiency, and neuropathy. There are several diabetic neuropathies, classified according to whether they are symmetric or asymmetric. Proximal motor neuropathy is an example of an asymmetric diabetic neuropathy. Symmetric diabetic neuropathies include autonomic neuropathy and diabetic distal polyneuropathy (DPN).

DPN is characterized by damage to the peripheral nerves. Nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution, but generally involve small fibers before the large ones. Symptoms and findings are usually symmetric and begin distally (feet and hands). Nerve damage is initially manifest as numbness, tingling, sharpness, burning, as well as loss of sensation in bandlike regions (commonly at the balls of the feet or tips of the toes) or on the soles of the feet. With disease progression, the loss of sensation can spread to both feet and the lower legs in a "stocking" fashion. Proprioceptive loss also occurs, manifest as unsteadiness of gait. Sensory loss in the hands is generally noted after loss of sensation is apparent at the level of the shins. Other sensory symptoms can include pain and hyperpathia. Pain is present at rest and is worse at night. Pain is often chronic, but subsides as the neuropathy progresses – indicative of worsening of diabetic disease and nerve damage. Patients can also develop motor findings in a graded manner, with loss of ankle and knee reflexes, weakness upon dorsiflexion of the toes and feet, and distal upper extremity weakness.

The mean time to DPN symptoms following diagnosis of diabetes is 8 years. Estimates of prevalence vary widely, due to discrepancies in diagnostic criteria and methods of patient selection and assessment. However, the literature shows that approximately 65% to 80% all patients with diabetes have DPN (based either on clinical or electrophysiologic exam). Disease progression can be slowed with aggressive blood glucose control.

One serious consequence of DPN is the development of foot ulcers. DPN is associated with a 7-fold increase in the risk of foot ulcers, generally in older patients with diabetes and occurring at the soles of the feet. The data show that among patients with diabetes, 15% develop a foot ulcer, and 12-24% of patients with a foot ulcer require amputation. Foot ulcers develop because DPN causes loss of protective sensation, as well as loss of proprioception and proper foot coordination, both of which increase mechanical stress on the foot. Patients are unaware of injury to their feet, or even sensory symptoms of common foot infections such as athlete's foot. What begins as a minor break in the skin can progress to a significant wound, especially in the presence of peripheral arterial insufficiency which delays wound healing.

Treatment of DPN begins with improved glycemic control, although this does not usually resolve the patient's symptoms. Symptomatic treatment is the mainstay of therapy, and providers prescribe such therapies as tricyclic antidepressants, gabapentin, NSAIDs, topical capsaicin, and carbamazepine. However, none of these drugs has yet shown efficacy in trials evaluated by the Agency.

**NDA Submission for Diabetic Peripheral Neuropathy**

The Sponsor submitted 5 trials in support of efficacy and safety of pregabalin as treatment for DPN. Additional supportive safety information was provided by 48 Phase 2/3 trials in other indications.

*Efficacy review*

Efficacy was evaluated in patients with a diagnosis of DPN for at least 1 year, evidence of glycemic control, mild renal impairment or normal renal function (CLcr > 60 mL/min), and treatment with acetaminophen for breakthrough pain only. Of note, there was only one efficacy trial that included subjects with moderate to severe renal impairment (CLcr 30 to 60 mL/min) – a total of 47 such patients were enrolled. Treatment with pregabalin varied from 6 to 8 weeks. The primary measure of drug effectiveness was the daily pain scores as assessed on an 11-point Likert-type numerical rating scale from 0 (“no pain”) to 10 (“worst pain”). A supporting measure of effectiveness was the proportion of responders in each treatment group. Three of the efficacy trials supported effectiveness of pregabalin, given as three divided doses of either 300- or 600 mg/day. The single trial in which subjects with a low CLcr were enrolled did not contribute to the finding of drug efficacy.

Protocol	Treatment Group	Δ in Pain Score	p Value	% Responders
014	Placebo	-0.98		12.9%
	600 mg	01.99	<0.001	29.3%
029	Placebo	-1.26		16.5%
	300 mg	-2.10	<0.001	38.3%
	600 mg	-2.20	<0.001	36.6%
131	Placebo	-0.59		7.14%
	300 mg	-1.79	0.001	32.9%

*Safety review*Non-clinical safety

Concerns regarding the toxicology of pregabalin are two: carcinogenicity (hemangiosarcomas in mice) and dermatopathy (skin lesions in rats and monkeys). This information is summarized in the accompanying slides. Background information is included for the angiosarcomas (Attachment A) and skin lesions (Attachment B).

*Carcinogenicity*

In the first mouse carcinogenicity study, groups of 65 B6C3F1 mice/sex were given 200, 1000, or 5000 mg/kg in the diet daily for 104 weeks. A dose-related increased incidence of hemangiosarcoma occurred in both sexes at 1000 and 5000 mg/kg. Hemangiosarcoma occurred in multiple tissue/organ sites, although they were most frequently observed in the liver, spleen, and bone marrow and correlated with clinical signs of internal palpable masses and gross pathologic findings of liver masses and enlarged spleens. Hemangiosarcoma was considered the cause of death in 1, 3, 13, and 13 males, and in 1,

3, 12, and 15 females in the controls and at 200, 1000, and 5000 mg/kg, respectively. The first hemangiosarcoma was diagnosed in a control female found dead at Week 49. The first hemangiosarcoma in a drug-treated group occurred in a male at 1000 mg/kg during Week 50. Hemangiosarcomas were primarily late in onset, with mean tumor latency across all groups of 88 to 102 weeks in males and 76 to 96 weeks in females.

To assess the carcinogenic potential of pregabalin in another mouse strain groups of 65 CD-1 mice/sex were given 200, 1000, or 5000 mg/kg in the diet daily for 104 weeks. Doses were the same as used previously in B6C3F1 mice. Of 27 tumor types in males and 45 tumor types in females, only hemangiosarcoma in males showed a statistically significant positive-dose trend in the Peto test. The number of tumor-bearing males was 2, 5, 6, and 14 at 0, 200, 1000, and 5000 mg/kg, respectively. There was a statistically significant difference at 5000 mg/kg when compared to untreated controls ( $p < 0.005$ ). In females, the numbers of animals with hemangiosarcoma were 6, 9, 10, and 13 at 0, 200, 1000, and 5000 mg/kg, respectively. There was a slight increase in tumor incidence with dose but the dose trend was not statistically significant ( $p = 0.0058$ ). Hemangiosarcomas occurred in multiple tissues of both males and females but were found most frequently in liver, spleen, and bone marrow. In females, hemangiosarcoma occurred most frequently in uterus at all doses. The first hemangiosarcoma was diagnosed in a female at 5000 mg/kg in Week 46 and the first in a control female at Week 47. Hemangiosarcomas were primarily late in onset with mean tumor latency across all groups of 90 to 104 weeks in males and 80 to 100 weeks in females. There were no differences between control and drug-treated animals in tumor onset or latency.

#### *Dermatopathy*

Skin lesions characterized clinically by a spectrum of lesions ranging from erythema to necrosis, and histologically by hyperkeratosis, acanthosis, fibrosis, and/or necrosis of the tail, were observed in rats given = 50 mg/kg in oral repeated-dose studies, with associated  $AUC_{(0-24)} = 241 \mu\text{g}\cdot\text{hr}/\text{mL}$ . Lesions typically appeared within the first 2 weeks of treatment at higher doses and resolved in most affected animals by Week 7 in the 13-week study and by Week 4 in the 52-week study. Similar skin lesions were observed in monkeys in oral repeated-dose studies, and were located primarily on the tail in most animals. In the chronic monkey study, lesions were observed at = 25 mg/kg, with plasma pregabalin  $AUC_{(0-24)}$  values =  $219 \mu\text{g}\cdot\text{hr}/\text{mL}$ . As in rats, lesions in affected animals in the chronic monkey study generally resolved prior to study termination. Subcutaneous tail temperature, used as an indirect measure of tail blood flow in the chronic monkey study, showed no consistent differences between control and high-dose animals, or between affected and unaffected animals within the same group. Pregabalin at 5% and 7.5% did not induce contact sensitization (allergic dermatitis) in rats in the local lymph node assay. The etiology of the skin lesions remains unknown. No tail dermatopathy was observed in mice given repeated oral doses of pregabalin up to 13 g/kg up to 13 weeks. Missing tail tips were observed in mice given up to 5000 mg/kg ( $AUC_{(0-24)}$  of  $3150 \mu\text{g}\cdot\text{hr}/\text{mL}$ ) in the B6C3F1 but not the CD-1 carcinogenicity study, however, the relationship of this lesion to dermatopathy in rats and monkeys is unknown.

*Clinical safety*

In light of the animal findings of hemangiomas and hemangiosarcomas, the safety data were reviewed to determine the frequency of neoplastic adverse events (AEs) in the safety database, and the consistency of these reports with angiosarcoma. Even though remarkable findings with respect to neoplasms were not expected, an analysis was conducted anyway, given that the dataset was large (8,666 subjects), and more than 200 patients had been exposed to the highest proposed dose (600 mg/day) for upwards of 2 years.

Due to the Sponsor's theory that hemangiosarcomas developed, in part, due to increased platelet activation and aggregation, as well as changes in platelet factors and growth factors, the data were reviewed for changes in platelet parameters. Only platelet counts were measured in clinical trials, so this was the only platelet parameter that was investigated.

Although the relevance of the preclinical findings of tail dermatopathy to humans was uncertain, there remained the potential for pregabalin-induced skin injury in patients with DPN. This population, as has already been described, is extremely vulnerable to the adverse sequelae of skin ulceration. Therefore, the safety data were examined for reports of skin-related adverse events, with a focus on skin ulcers.

Lastly, the safety data were assessed for the frequency of vision-related adverse events. During Phase I trials, some subjects reported temporary vision abnormalities, and formal vision testing was added to clinical trials. Vision changes were of concern, given that around the time that Phase I trials were being conducted, Vigabatrin, a GABA-transaminase inhibitor, was found to cause non-reversible visual field defects. The ophthalmologic test data were reviewed to determine whether there was evidence of pregabalin-related effects on the visual system.

*Neoplasms*

Of the total exposed population, 70 subjects (0.8%) developed at least one neoplasm. Most tumors were described as "polyps" and were considered "non-serious." Eight neoplasms were described as serious, and included 1 case each of an eye mass, a corpus polyp, nasal polyps, ethmoid polyps, as well as 4 cases of renal tumors (including 1 case of a bleeding angioleiomyoma). Additionally, 1 patient reported cherry angiomas and another developed "angiomas." Neither case was considered serious. There were 4 unspecified and non-serious face/scalp tumors, and no hepatic tumors.

*Platelets*

Analysis of the mean change from baseline showed a decrease in platelets among pregabalin-treated patients, compared to placebo patients. Pregabalin patients had a mean decrease of  $9.5 \times 10^3/\mu\text{L}$ , whereas placebo patients had a decrease that was essentially negligible ( $0.3 \times 10^3/\mu\text{L}$ ). The effect on platelet count appeared to be dose-dependent. Analysis of data from only DPN controlled trials also showed a decrease in platelets. However, the dose-response effect was less evident. No studies of platelet

activation or aggregation were conducted in clinical trials. Therefore the mechanism by which the platelet count was decreased is as yet unknown.

#### *Dermatological changes*

Skin ulcer was the second most common skin-related adverse event (n = 45) in the DPN population. The majority of skin ulcers were located on the foot, ankle, or lower extremity. Additional locations of ulcers were the groin, scrotum and abdomen (n = 1 each). Only 7 ulcers were categorized as 'serious.' Review of the narratives for these cases found that each had an alternate possible cause for the development and/or worsening of the skin ulcer.

In the short-term (6-12 week), controlled DPN studies, there was no difference in the percent of subjects who reported a skin ulcer between the placebo group and the pregabalin group (0.4% vs. 0.3%, respectively). Since these were very brief studies, data from open-label extension studies were examined to see whether there might be a signal of increased risk of skin ulcers among pregabalin-exposed subjects.

The open-label studies used a titration design and allowed dose adjustments throughout the period of participation, which could have been as long as 2 years. Most people were titrated to target doses of 300 mg/day or 600 mg/d, but various intermediate doses were used at different times. Dose at onset of adverse event was used to explore dose dependency, although that is to some degree a reflection of time on study, particularly at lower doses. When the number of people who reported skin ulcers, by dose at onset, was examined, there was suggestion that the frequency was highest among patients who were taking 600 mg/d or higher, and that some dose-dependence was apparent. Further analysis, taking into duration of drug exposure, showed no considerable difference in the frequency of skin ulcers across drug groups. Consequently, we were unable to establish an association between pregabalin treatment and skin ulcers in the DPN population. However, in the absence of a comparator group exposed to drug for a similar duration as the pregabalin group, we cannot fully rule out the possibility of a real effect.

#### *Vision abnormalities*

The combined data (i.e. data from all indications) from all controlled trials show that a greater proportion of pregabalin-treated patients reported changes in visual acuity, and visual fields than did placebo patients. Dose dependency was suggested for loss of visual acuity and vision "abnormal vision." When a similar analysis was conducted for only DPN controlled trials, the data showed that loss of visual acuity (verbatim term "blurry vision") and "abnormal vision" were more frequent in DPN pregabalin-treated patients, and appeared to be dose-dependent. There did not appear to be a considerable difference between pregabalin and placebo groups with respect to visual field defects.

	Placebo N = 459 n (%)	Pregabalin All doses N = 979 n (%)	Pregabalin 150 mg/day N = 212 n (%)	Pregabalin 300 mg/day N = 321 n (%)	Pregabalin 600 mg/day N = 369 n (%)
Abnormal vision	1 (0.22)	11 (1.12)	1 (0.47)	4 (1.24)	5 (1.36)
Decreased visual acuity	7 (1.53)	35 (3.58)	3 (1.42)	9 (2.80)	5 (1.36)
Diplopia	0	8 (0.82)	2 (0.94)	4 (1.24)	1 (0.27)
Decreased visual field	5 (1.09)	6 (0.61)	3 (1.42)	1 (0.31)	2 (0.54)

Dr. Wiley Chambers (HFD 550) reviewed the ophthalmological data from clinical trials. Unfortunately, there was insufficient detail regarding vision testing as well as information on how tests were conducted to distinguish a real effect of pregabalin on the visual system. Nevertheless, the available data show that there are slowly developing vision changes, some minor, associated with pregabalin treatment. The degree of persistence of the findings is unclear from the data. Contrary to what might be expected, there were a greater number of events in the 300 mg/day group than in the 600 mg/day group

The effects of pregabalin on vision function among patients with DPN were examined. Pregabalin does have an adverse effect, but this appears to be different from the typical changes associated with diabetic retinopathy. Again, there is insufficient information to determine if the pregabalin-associated changes add to the vision abnormalities and morbidity already experienced by the diabetic population

Nevertheless, co-occurrence of the loss of visual acuity and the visual field defects suggests a retinal process secondary to drug exposure. Also, because Pfizer conducted "super-threshold" visual testing and abnormalities were found anyway, it is likely that pregabalin does have an effect on vision.

#### Issues

- The preclinical data show that pregabalin is carcinogenic in mice. The Sponsor states that this is species-specific but, despite exhaustive testing, has not been able to support this assertion.
- The dermatopathy seen in animals creates concern that pregabalin could contribute to skin breakdown in humans, although no clinical correlation has been identified in the available data.
- The clinical data demonstrate an effect of pregabalin on visual acuity based on adverse event reports. However, the visual effects of the drug have not been well-characterized due to inadequacies of the formal testing included in the development program.
- Together, the possibility of drug-related effects on skin integrity and the as-yet poorly characterized effects of pregabalin represent a concerning level of risk in the diabetic population, which is at particular risk of morbidity related to both of these effects.

Furthermore, because of diabetes-induced renal impairment, this population may be at risk of developing drug-related adverse events when using this renally-cleared product.

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**Questions for the Panel**

1. We believe that the relevance of the preclinical carcinogenic findings to humans cannot be ruled out and that the risk of drug-associated cancer should be included in the labeling. Does the Panel agree?
2. We propose that the dermatologic and ophthalmologic effects of pregabalin should be better characterized prior to approval in order to establish that the risk/benefit ratio is favorable in the diabetic population. Does the panel agree?

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# **Appendix A**

## **Sponsor's Summary of Carcinogenicity Data**

(H & E) stained sections (Table 2.6.7.17C, RR 745-03431).<sup>227</sup> Cmax and AUC(0-24) increased less than proportionally to dose, and no sex differences were apparent (Table 26).

**Table 26. Toxicokinetic Parameters in Mice Given Pregabalin Daily in the Diet for 13 Weeks<sup>a</sup>**

Dose (mg/kg)	Male		Female	
	Cmax	AUC(0-24)	Cmax	AUC(0-24)
1000	45.5	828	90.5	967
4000	147	2460	163	2830
8000	202	4450	411	5870

Table 2.6.7.10A, RR 764-02611 appended to RR 250-01744.

Cmax = Maximum plasma concentration ( $\mu\text{g/mL}$ ); AUC(0-24) = Area under the plasma concentration-time curve from 0 to 24 hours ( $\mu\text{g}\cdot\text{hr/mL}$ ).

<sup>a</sup> Samples obtained 0, 2, 4, 8, 12, and 24 hours after initiation of the dark cycle during Week 13; each drug-treated animal used for 1 time point. A single concentration-time curve was constructed from the mean of individual plasma drug concentrations at each sampling time; N = 3/time point.

#### 2.6.6.5.2. Pivotal Studies

##### 2.6.6.5.2.1. B6C3F1 Mouse

To assess the carcinogenic potential of pregabalin, B6C3F1 mice were given 200, 1000, or 5000 mg/kg in the diet daily for 104 weeks (Table 2.6.7.10B, RR 745-03275).<sup>251</sup> Doses were based on results of the 13-week study in mice, and in accordance with recommendations of the US FDA. No dose-limiting toxicity was seen in the 13-week study up to 8000 mg/kg. Therefore, 5000 mg/kg was selected as the highest dose to achieve an AUC(0-24) at least 25 times the mean human exposure at the maximum recommended clinical dose, and in accordance with ICH guidelines for nongenotoxic pharmaceuticals with low organ toxicity. The low and mid doses were selected to achieve a 5-fold separation of doses and result in AUC(0-24) values equivalent to and approximately 5 times the mean human exposure, respectively.

An increased incidence of distended abdomen was noted in males at 200 and 1000 mg/kg and in females at all doses. An increased incidence of internal palpable masses in the abdominal region was present in males at 1000 and 5000 mg/kg and in females at 5000 mg/kg. These findings appeared after Week 52. Staining of the anogenital region was seen in males at 1000 and 5000 mg/kg and an increased incidence of missing tail tips occurred in both sexes at all doses.

Body weight increased 15% to 31% at termination in all treated groups compared to controls, but the increases were not dose-related. The increase in body weight began during the first month and persisted throughout the study. Food consumption increased 4% to 37% in both sexes at all doses. No ophthalmic findings were noted. Platelet count increased 35% and 33% in males at 1000 and 5000 mg/kg, respectively, and 36%, 32%, and 58% in females at 200, 1000, and 5000 mg/kg, respectively.

An increased incidence of liver masses was noted at necropsy in males at 1000 and 5000 mg/kg and in females at all doses. Enlarged spleen was observed in males at the same doses and in females at 1000 mg/kg. Testes weight decreased 20% at 5000 mg/kg and liver weight increased 24% to 46% in females at all doses.

Nonneoplastic histopathologic findings were noted in spleen, testes, and urinary bladder. Increased splenic EMH was noted in males at 1000 mg/kg and in both sexes at 5000 mg/kg. The increased incidence of testicular degeneration at 5000 mg/kg was consistent with a spontaneous age-related change since the severity of the lesion was minimal in most animals at this dose. In addition, testicular degeneration in the only 3 animals with severe lesions was unilateral, consistent with age-related, spontaneous changes. An increased incidence of urinary bladder dilatation also was observed in males at 5000 mg/kg and correlated with the clinical observation of urine staining.

A dose-related decrease in survival was observed in males and females at 1000 and 5000 mg/kg. Overall survival at Week 104 for the control, 200-, 1000-, and 5000- mg/kg groups were 88%, 80%, 62%, and 34% in males, and 69%, 68%, 44%, and 38% in females, respectively. Survival at Week 80 was 97%, 94%, 80%, and 73% in males and 91%, 86%, 77%, and 74% in females in controls and at 200, 1000, and 5000 mg/kg, respectively. These data met the criteria for a valid study (>50% survival in all groups at Week 80) as defined by Lin and Ali.<sup>246</sup>

Of 34 tumor types in males and 41 tumor types in females, there were 6 tumor categories in each sex that showed a statistically significant positive dose trend in the Peto test as indicated in Table 27 and the incidence of these tumors is presented in Table 28.

**Table 27. Tumor Categories With Statistically Significant Peto Test for Dose Trend**

Tumor Type	Trend Direction	Peto Test Two-Tailed p-Value
<b>Males</b>		
All Tumors	+	<0.001
All Malignant Tumors	+	<0.001
Adenoma of Adrenal Gland, Cortex (Benign)	+	0.012
Hemangioma of Bone Marrow, Femur (Benign)	+	0.012
Interstitial Cell Tumor of Testis (Benign)	+	0.050
Hemangiosarcoma <sup>a</sup>	+	<0.001
<b>Females</b>		
All Tumors	+	0.001
All Malignant Tumors	+	0.001
A Cell Carcinoma of Adrenal Gland, Cortex (Malignant)	+	0.035
Leiomyoma of Large Intestine, Cecum (Benign)	+	0.033
Adenoma of Mammary Gland (Benign)	+	0.040
Hemangiosarcoma <sup>a</sup>	+	<0.001

<sup>a</sup> Multiple tissue sites

**Table 28. Number of Tumor-Bearing Animals for Tumor Types With Statistically Significant Peto Test for Positive-Dose Trend**

Sex	Tumor Type	CI-1008 Dose (mg/kg)			
		0	200	1000	5000
M	All Tumors	34	36	48	38
M	All Malignant Tumors	18	16	36	28
M	Adenoma of Adrenal Gland, Cortex (Benign)	0	0	0	1
M	Hemangioma of Bone Marrow, Femur (Benign)	0	0	0	1
M	Interstitial Cell Tumor of Testis (Benign)	0	0	0	1
M	Hemangiosarcoma <sup>a</sup>	2	3	19	22
F	All Tumors	44	45	51	45
F	All Malignant Tumors	24	30	40	35
F	A Cell Carcinoma of Adrenal Gland, Cortex (Malignant)	0	0	0	1
F	Leiomyoma of Large Intestine, Cecum (Benign)	0	0	0	1
F	Adenoma of Mammary Gland (Benign)	1	0	0	3
F	Hemangiosarcoma <sup>a</sup>	2	7	19	25

<sup>a</sup> Multiple tissue sites

When analyzed by the exact trend test, there were no statistically significant positive dose trends for any of the tumor categories with  $\leq 12$  tumor-bearing animals. The p-values are presented in Table 29.

**Table 29. Results of Exact Trend Test**

Tumor Category	p-Value for Exact-Trend Test
Adenoma of Adrenal Gland, Cortex	0.131
Hemangioma of Bone Marrow, Femur	0.129
Interstitial Cell Tumor of the Testis	0.200
A Cell Carcinoma of Adrenal Gland, Cortex	0.177
Leiomyoma of Large Intestine, Cecum	0.175
Adenoma of Mammary Gland	0.028

Therefore, the only tumor categories for which there were statistically significant positive-dose trends were all tumors, all malignant tumors, and hemangiosarcoma. When hemangiosarcomas were excluded, the incidence of all malignant tumors was 16, 13, 17, and 6 in males, and 22, 23, 21, and 10 in females, at 0, 200, 1000, and 5000 mg/kg, respectively. These data clearly demonstrate the positive-dose trend for all malignant tumors was due to hemangiosarcoma.

A dose-related increased incidence of hemangiosarcoma occurred in both sexes at 1000 and 5000 mg/kg. Hemangiosarcoma occurred in multiple tissue/organ sites, although they were most frequently observed in the liver, spleen, and bone marrow and correlated with clinical signs of internal palpable masses and gross pathologic findings of liver masses and enlarged spleens. Hemangiosarcoma was considered the cause of death in 1, 3, 13, and 13 males, and in 1, 3, 12, and 15 females in the controls and at 200, 1000, and 5000 mg/kg, respectively. The first hemangiosarcoma was diagnosed in a control female found dead at Week 49. The

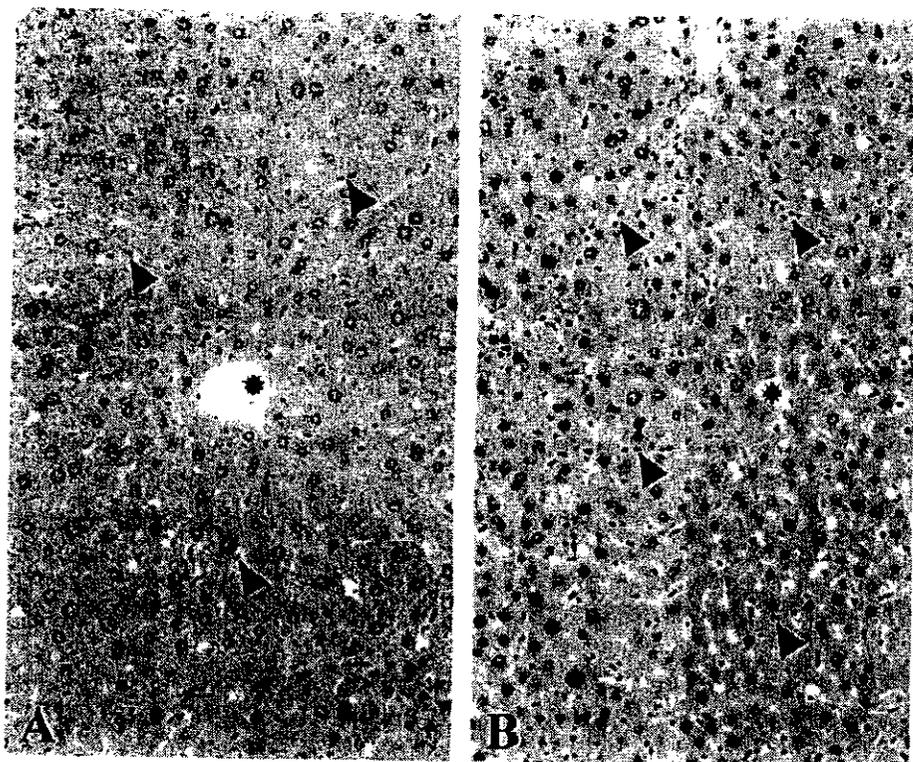
first hemangiosarcoma in a drug-treated group occurred in a male at 1000 mg/kg during Week 50. Hemangiosarcomas were primarily late in onset with a mean tumor latency across all groups of 88 to 102 weeks in males and 76 to 96 weeks in females.

When analyzed by the Fisher's exact test, there was no statistically significant difference between the incidence of hemangiosarcomas in the low dose versus the controls in either sex ( $p = 0.485$  for males;  $p = 0.098$  for females), indicating no increase in hemangiosarcoma at 200 mg/kg.

Based on the increased incidence of hemangiosarcoma in this study, a retrospective histopathologic examination of target organs (liver, spleen and bone/bone marrow) and nontarget organs (lung, kidney, and lymph node) for proliferative vascular lesions and other nonneoplastic changes was conducted (Table 2.6.7.10B, RR 745-03454).<sup>252</sup> The incidence of minimal to mild hepatic sinusoidal cell hyperplasia was increased at 200 and 1000 mg/kg (Figure 1). The lower incidence of this finding at 5000 mg/kg may be related to increased mortality at that dose. Sinusoidal cell hyperplasia likely represents proliferation of Kupffer and/or endothelial cells, but cell types involved could not be differentiated in the H&E stained sections. Increased splenic hematopoiesis previously reported was confirmed.

**Figure 1. Hematoxylin and Eosin Staining of Liver in a Control Mouse (A) and a Mouse Given 1000 mg/kg (B) for 2 Years**

Central vein indicated by asterisk (\*). Examples of sinusoidal cells (endothelial and Kupffer cells) are labeled by arrowheads. Sinusoidal cell hyperplasia is evident in pregabalin-treated mice.

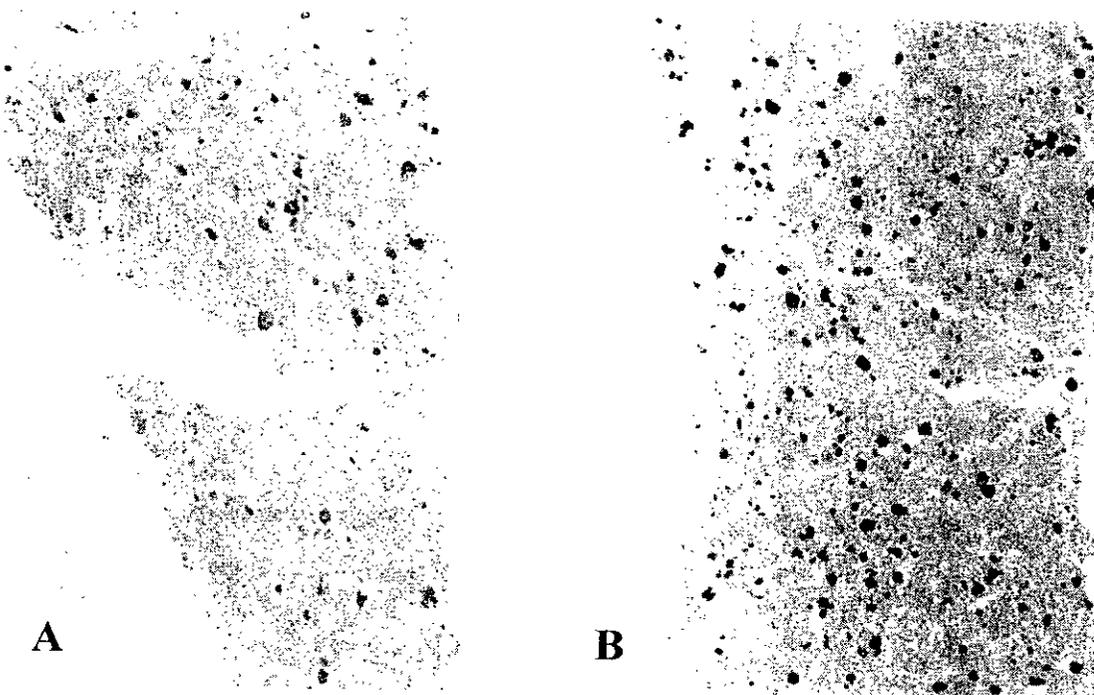


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A dose-related increased incidence of megakaryocytic hypercellularity was noted in both sexes that correlated with a retrospective quantitative evaluation of bone marrow megakaryocytes. Total megakaryocytes in femoral bone marrow (sternal if necessary) increased 52%, 79%, and 104% in males and 38%, 66%, and 83% in females at 200, 1000, and 5000 mg/kg, respectively (Figure 2, Table 30) (Table 2.6.7.10B, RR 745-03456).<sup>253</sup>

**Figure 2. Immunohistochemical Staining of Bone Marrow for Von Willebrand Factor (Factor VIII) on Megakaryocytes in a Control Mouse (A) and a Mouse Given 5000 mg/kg (B) for 2 Years**

Increased numbers of megakaryocytes (brown-stained cells) are evident in pregabalin-treated mice.



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**Table 30. Total Megakaryocytes in B6C3F1 Mouse Bone Marrow**

Dose (mg/kg)	Males		Females	
	N	Count <sup>a</sup>	N	Count <sup>a</sup>
UC	65	43.2 ± 1.38	62	43.0 ± 1.36
200	63	65.8 ± 2.26†	66	60.1 ± 2.53†
1000	64	77.3 ± 2.50†	62	71.2 ± 2.40†
5000	61	88.3 ± 3.37†	63	78.9 ± 2.49†

Table 2.6.7.10B, RR 745-03456

N = Number of animals; UC = Untreated control.

† Significant trend test at 0.02 (0.005 for quadratic) level of significance.

<sup>a</sup> Total count/5000 hematopoietic cells; mean ± standard error.

Retrospective review of peripheral blood smears from this study revealed a dose-related increase in RBC and platelet morphologic abnormalities (Table 31) (Table 2.6.7.10B, RR 745-03714).<sup>254</sup> The predominant RBC abnormality was the presence of schistocytes. Platelet abnormalities consisting of bizarre shape change with numerous pseudopodia, central condensation of platelet granules, platelet swelling, hypogranulation, and the presence of platelet aggregates undergoing partial to complete degranulation were consistent with the process of platelet activation. Giant platelets that reached the size of erythrocytes were also increased in a dose-dependent manner. Presence of giant platelets suggests increased platelet turnover; whereas other platelet abnormalities are consistent with in vivo platelet activation.

**Table 31. Peripheral Blood Abnormalities in B6C3F1 Mice Given Pregabalin for 2 Years**

Dose (mg/kg)	N	Nonuniform Platelet Size (%)	Giant Platelets (%)	Platelet Aggregates (%)	Schistocytes (%)
<b>Male</b>					
UC	53	15.1	1.9	1.9	1.9
200	47	12.8	2.1	8.5	2.1
1000	36	75.0	63.9	13.9	16.7
5000	17	100.0	100.0	29.4	41.2
<b>Female</b>					
UC	42	19.0	2.4	2.4	2.4
200	41	17.1	4.9	7.3	4.9
1000	27	44.4	22.2	18.5	11.1
5000	23	91.3	52.2	30.4	26.1

Table 2.6.7.10B, RR 745-03714

UC = Untreated control.

These findings of peripheral blood morphologic changes, megakaryocytic hyperplasia in bone marrow, and sinusoidal cell hyperplasia in liver may be related to the mechanism of hemangiosarcoma formation. Accordingly, additional studies were conducted in B6C3F1 mice to determine the cell type(s) involved in the liver sinusoidal cell hyperplasia (see Section 2.6.6.5.4.2.2.2).

The incidence of pulmonary macrophage infiltrates and/or granulomatous inflammation increased in drug-treated groups. Pulmonary lesions were typically focal/multifocal and minimal to mild in severity. Pulmonary macrophage infiltrates and/or lipid granulomas are seen spontaneously in aging mice. There was no apparent relationship between drug treatment and incidence of pulmonary neoplasia in this study. Therefore, these nonneoplastic pulmonary changes were not considered relevant for carcinogenicity. There were no proliferative nonneoplastic findings in lymph nodes or kidney.

Pregabalin toxicokinetic parameters at doses used in this 2-year study were assessed in B6C3F1 mice given the same doses in the diet for 4 weeks (Table 32) (Table 2.6.7.10B, RR 745-03239, RR 764-03533).<sup>255,256</sup> Mean Cmax and AUC(0-24) increased approximately linearly with dose in both sexes.

**Table 32. Toxicokinetic Parameters in B6C3F1 Mice Given Pregabalin Daily in the Diet for 4 Weeks<sup>a</sup>**

Dose (mg/kg)	Male			Female		
	4 Hour	Cmax	AUC(0-24)	4 Hour	Cmax	AUC(0-24)
200	6.24 ± 2.12	10.9	153	8.69 ± 1.67	9.06	140
1000	38.0 ± 7.77	50.6	653	42.6 ± 7.39	42.6	802
5000	130 ± 81.9	215	3830	209 ± 28.9	209	3840

Table 2.6.7.10B, RR 745-03239, RR 764-03533

Cmax = Maximum plasma concentration (µg/mL); AUC(0-24) = Area under the plasma concentration-time curve from 0 to 24 hours (µg hr/mL)

<sup>a</sup> Samples obtained 2, 4, 6, 8, 12, and 24 hours after initiation of the dark cycle in Week 4; each animal used for 1 time point. A single concentration-time curve was constructed from the mean of individual plasma drug concentrations at each sampling time; N = 4/time point.

To monitor pregabalin exposure, plasma samples were obtained from mice after 104 weeks of dosing (Table 33) (Table 2.6.7.10B, RR 764-03532).<sup>257</sup> Concentrations 4 hours after initiation of the dark cycle after 104 weeks were similar to those observed at the 4-hour time point in the supportive toxicokinetic study and suggest the toxicokinetic profile does not change appreciably after 104 weeks of dosing.

**Table 33. Plasma Concentrations in B6C3F1 Mice Given Pregabalin Daily in the Diet for 104 Weeks<sup>a</sup>**

Dose (mg/kg)	Male	Female
200	4.55 ± 1.01	5.83 ± 2.64
1000	21.5 ± 14.2	48.0 ± 68.3
5000	98.8 ± 73.6	139 ± 69.7

Table 2.6.7.10B, RR 764-03532

<sup>a</sup> Samples obtained 4 hours after initiation of the dark cycle after 104 weeks (µg/mL); mean ± standard deviation; N = 5.

In summary, dietary administration of pregabalin to mice for 2 years at doses of 200, 1000, or 5000 mg/kg resulted in a statistically significant increase in hemangiosarcoma in both sexes at 1000 and 5000 mg/kg. Systemic exposure at the 2 highest doses were approximately 5 and 32 times the mean human exposure at the maximum recommended clinical dose, respectively. Pregabalin did not induce a carcinogenic response at 200 mg/kg with systemic exposure approximately equal to the mean human exposure at the maximum recommended clinical dose.

#### 2.6.6.5.2.2. CD-1 Mouse

To assess the carcinogenic potential of pregabalin in another mouse strain and evaluate reproducibility of findings from a previous study, CD-1 mice were given 200, 1000, or 5000 mg/kg in the diet daily for 104 weeks (Table 2.6.7.10C, RR 745-03610).<sup>258</sup> Doses were the same as used previously in B6C3F1 mice.

An increased incidence of distended abdomen was noted in males and females at 1000 and 5000 mg/kg. Staining of the urogenital region was seen in males at 1000 and 5000 mg/kg and in females at 1000 mg/kg. Hunched posture occurred in females at all doses and in males at 5000 mg/kg. There was no effect of treatment on the incidence of palpable masses and there were no ophthalmic findings.

Body weight increased 9% to 21% in Weeks 98 or 102 at all doses in both sexes compared to controls, but the increases were not dose-related. Body weight gain increased 31% to 146% in these groups during the first year of the study but was not different from controls through the remainder of the study. Nondose-related increases in food consumption ranging from 5% to 22% occurred in these groups beginning in Week 17 in males and Week 25 in females, and continued throughout the study. Mean red cell volume increased 5% and 8% in males at 1000 and 5000 mg/kg, respectively, and mean cell hemoglobin increased 7% in males at 5000 mg/kg. There were no drug-related effects on platelet count at Week 65/66 or Week 78/79. At termination, platelet count increased 32% in males at 5000 mg/kg. Mean platelet volume increased 3% to 5% in males at all doses and 3% in females at 1000 mg/kg.

At termination, testes weight relative to body weight decreased 16% at 1000 and 5000 mg/kg. In females, absolute and relative liver weights increased 16% to 59% at all doses and absolute and relative kidney weights increased 10% to 32% at 1000 and 5000 mg/kg. There were no apparent histopathologic correlates to the organ weight changes.

The only nonneoplastic finding was an increased incidence and severity of alveolar macrophage infiltration with associated changes, such as cholesterol cleft formation and perivascular, lymphoid cell infiltration, in females at 5000 mg/kg. Alveolar macrophage infiltration is a spontaneous age-related finding in rodents that was exacerbated by treatment. The clinical significance of the lesion is unknown. It was not associated with an increased incidence of lung tumors and did not appear a likely cause of increased mortality in these animals.

Overall survival at Week 104 in the control, 200, 1000, and 5000 mg/kg groups was 51%, 48%, 42%, and 43%, respectively, in males. In females, survival at Week 104 in control, 200, and 1000 mg/kg groups was 43%, 46%, and 42%, respectively. Since mortality was greatest in females at 5000 mg/kg than in other groups, the 21 survivors in this group were necropsied at Week 100 to ensure adequate tissue preservation for histopathologic analysis. Survival at Week 100 was 32%. Given the 100-week duration of exposure in this group, early termination was judged to have negligible impact on the carcinogenicity assessment. There was no statistically significant dose trend in mortality (accidental deaths excluded). Survival at Week 80 in the control, 200-, 1000-, and 5000-mg/kg dose groups was 85%, 83%, 74%, and 75% in males, and 74%, 78%, 75%, and 68% in females, respectively. These data meet the criteria for a valid study (>50% survival at Week 80) as defined by Lin and Ali.<sup>246</sup> Of 27 tumor types in males and 45 tumor types in females, only hemangiosarcoma in males showed a statistically significant positive-dose trend in the Peto test. The number of tumor-bearing males was 2, 5, 6, and 14 at 0, 200, 1000, and 5000 mg/kg, respectively. There was a statistically significant difference at 5000 mg/kg when compared to untreated controls ( $p < 0.005$ ). In females, the number of animals with hemangiosarcoma was 6, 9, 10, and 13 at 0, 200, 1000, and 5000 mg/kg, respectively. There was a slight increase in tumor incidence

with dose but the dose trend was not statistically significant ( $p = 0.0058$ ). Hemangiomas occurred in multiple tissues of both males and females but were found most frequently in liver, spleen, and bone marrow. In females, hemangiosarcoma occurred most frequently in uterus at all doses. The first hemangiosarcoma was diagnosed in a female at 5000 mg/kg in Week 46 and the first in a control female at Week 47. Hemangiosarcomas were primarily late in onset with a mean tumor latency across all groups of 90 to 104 weeks in males and 80 to 100 weeks in females.

In a retrospective quantitative evaluation of bone marrow, megakaryocytes in femoral bone marrow increased 18%, 43%, and 108% in males and 39%, 80%, and 80% in females at 200, 1000, and 5000 mg/kg, respectively (Table 34) (Table 2.6.7.10C, RR 745-03692).<sup>259</sup> Additional findings noted in pregabalin-treated mice were a predominantly erythroid environment as opposed to myeloid hyperplasia in untreated controls, an increase in megakaryocytes containing mitotic figures, and infiltrates of activated macrophages containing phagocytized debris (hemocyanin or hemosiderin) or erythrocytes. An extreme predominance of myeloid cells was a common occurrence in CD-1 control animals at termination of the 2-year study. The percentage of animals affected was 48% in males and 56% in females. In contrast, a predominantly erythroid environment was observed in pregabalin-treated animals. Myeloid hyperplasia was 39%, 15%, and 9% in males and 40%, 7%, and 9% in females at 200, 1000, and 5000 mg/kg, respectively. The incidence of megakaryocytes with mitotic figures in pregabalin-treated CD-1 mice was 3%, 14%, and 22% in males and 10%, 22%, and 28% in females at 200, 1000, and 5000 mg/kg, respectively, and  $\leq 2\%$  in controls. The incidence of activated macrophages with phagocytized debris was 23%, 44%, and 56% in males and 40%, 54%, and 50% in females at 200, 1000, and 5000 mg/kg, respectively, and  $\leq 18\%$  in controls.

**Table 34. Total Megakaryocytes in CD-1 Mouse Bone Marrow**

Dose (mg/kg)	Males		Females	
	N	Count <sup>a</sup>	N	Count <sup>a</sup>
UC	59	37.6 ± 1.75	57	28.4 ± 1.27
200	61	44.4 ± 2.29	62	39.6 ± 2.15†
1000	59	53.7 ± 3.32†	59	51.2 ± 2.14†
5000	55	78.2 ± 3.91†	54	51.2 ± 2.41†

Table 2.6.7.10C, RR 745-03692

N = Number of animals; UC = Untreated control.

† Significant trend test at the 0.02 (0.005 for quadratic) level of significance.

<sup>a</sup> Total count/5000 hematopoietic cells; mean ± standard error.

Retrospective review of peripheral blood smears from this study revealed similar findings at 5000 mg/kg as in the 2-year carcinogenicity study in B6C3F1 mice at all doses, but the incidence was lower (Table 35) (Table 2.6.7.10C, RR 745-03714).<sup>254</sup>

**Table 35. Peripheral Blood Abnormalities in CD-1 Mice Given Pregabalin for 2 Years**

Dose (mg/kg)	N	Nonuniform Platelet Size (%)	Giant Platelets (%)	Platelet Aggregates (%)	Schistocytes (%)
<b>Male</b>					
UC	46	2.2	2.2	4.3	0.0
200	38	0.0	5.3	7.9	5.3
1000	39	10.3	0.0	5.1	2.6
5000	39	66.7	46.2	17.9	10.3
<b>Female</b>					
UC	49	2.0	2.0	4.0	2.0
200	48	16.7	0.0	0.0	8.3
1000	47	25.5	8.5	12.8	4.3
5000	45	20.0	17.8	4.4	11.1

Table 2.6.7.10C, RR 745-03714

N = Number of animals; UC = Untreated control.

Pregabalin toxicokinetic parameters at doses used in this study were assessed in CD-1 mice given the same doses in the diet for 4 weeks (Table 36) (Table 2.6.7.10C, RR 745-03556, 764-04020).<sup>260,261</sup> Mean C<sub>max</sub> and AUC(0-24) increased approximately linearly with dose in both sexes.

**Table 36. Toxicokinetic Parameters in CD-1 Mice Given Pregabalin Daily in the Diet for 4 Weeks<sup>a</sup>**

Dose (mg/kg)	Male			Female		
	4 Hour	C <sub>max</sub>	AUC(0-24)	4 Hour	C <sub>max</sub>	AUC(0-24)
200	4.84 ± 1.21	8.72	105	6.00 ± 1.06	7.89	115
1000	42.7 ± 6.05	42.7	541	43.5 ± 0.978	43.5	558
5000	191 ± 55.4	218	3440	174 ± 40.2	174	3150

Table 2.6.7.10C, RR 745-03556, RR 764-04020

C<sub>max</sub> = Maximum plasma concentration (µg/mL); AUC(0-24) = Area under the plasma concentration-time curve from 0 to 24 hours (µg·hr/mL).

<sup>a</sup> Samples obtained 2, 4, 6, 8, 12, and 24 hours after initiation of the dark cycle in Week 4; each animal used for 1 time point. A single concentration-time curve was constructed from the mean of individual plasma drug concentrations at each sampling time; N = 4/time point.

To monitor pregabalin exposure, plasma samples were obtained from mice after 104 weeks of dosing (Table 37) (Table 2.6.7.10C, RR 764-04054).<sup>262</sup> Concentrations 4 hours after initiation of the dark cycle after 104 weeks were similar to those observed at the 4-hour time point in the supportive toxicokinetic study and suggest the toxicokinetic profile does not change appreciably after 104 weeks of dosing.

**Table 37. Plasma Concentrations in CD-1 Mice Given Pregabalin Daily in the Diet for 104 Weeks<sup>a</sup>**

Dose (mg/kg)	Male	Female
200	14.3 ± 3.15	11.0 ± 1.92
1000	49.7 ± 9.54	61.9 ± 24.0
5000	429 ± 213	473 <sup>b</sup> ± 170

Table 2.6.7.10C, RR 764-04054 appended to RR 745-03610.

<sup>a</sup> Samples obtained 4 hours after initiation of the dark cycle after 104 weeks ( $\mu\text{g/mL}$ ); mean  $\pm$  standard deviation; N = 5.

<sup>b</sup> Samples obtained after Week 100.

In summary, dietary administration of pregabalin to CD-1 mice for 2 years at doses of 200, 1000, or 5000 mg/kg resulted in a statistically significant increase in hemangiosarcomas in males at 5000 mg/kg. Systemic exposure was 28 times the mean human exposure at the maximum recommended clinical dose. Although not statistically significant, there was an increased incidence of hemangiosarcoma in females at 5000 mg/kg.

#### 2.6.6.5.2.3. Wistar Rat

##### 2.6.6.5.2.3.1. First Study

To assess the carcinogenic potential of pregabalin, male Wistar rats were given 50, 150, or 450 mg/kg and female Wistar rats were given 100, 300, or 900 mg/kg in the diet daily for 104 weeks (Table 2.6.7.10D, RR 745-03274).<sup>263</sup> Doses were based on toxicity endpoints from 13- and 52-week studies in rats and in accordance with recommendations of the US FDA. The highest doses of 450 mg/kg in males and 900 mg/kg in females were based on the difference in magnitude of body weight changes in these studies. The low and mid doses were based on exposure multiples of approximately 1 to 8 times the mean human exposure at the maximum recommended clinical dose.

An increased incidence of urine staining occurred in males at 150 and 450 mg/kg and in females at all doses. Palpable masses occurred similarly between control and treated rats. At Week 104, body weight decreased 13% and 24% and body weight gain decreased 22% and 41% in males at 450 mg/kg and in females at 900 mg/kg, respectively. Food consumption throughout the study decreased 5% to 21% in males and females at these doses. At 50 mg/kg in males and 100 mg/kg in females, body weight and food consumption increased up to 16% compared to controls throughout the study. Body weight and food consumption were unaffected in males at 150 mg/kg and in females at 300 mg/kg. No ophthalmic findings were noted.

RBC count increased 9% and 12% and platelet count decreased 14% and 20% in males at 150 and 450 mg/kg, respectively, at termination. At termination in females, RBC count increased 8% to 14% at all doses and Hct increased 6% at 900 mg/kg. Platelet count decreased 12% and 19% at 300 and 900 mg/kg, respectively. In a retrospective quantitative evaluation of bone marrow, megakaryocytes in femoral bone marrow (sternal if necessary)

## **Appendix B**

### **Sponsor's Summary of Dermatopathy Data**

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## **INFORMATION REQUEST – PHARMACOLOGY TOXICOLOGY**

### **Request 1: Submit legible photograph-quality images of tail lesions of both species.**

Improved images of tail alterations noted in-life in rats administered pregabalin orally (Study 1554; RR 250-01722) are submitted as Figures F-1 to F-4, and in monkeys administered pregabalin orally (Study 1992; RR 745-02559) are submitted as Figures F-5 to F-8.

### **Request 2: Submit any additional information you may have or are able to obtain regarding the etiology/pathology of the lesions.**

Dermatopathy was noted in rats and monkeys in pivotal repeated-dose oral toxicity studies, and relevant study findings are summarized in respective sections below. Dermatopathy comprised a spectrum of clinical signs, gross observations made at necropsy, and histopathology. All information pertaining to our current understanding of the etiology/pathology of the lesions has been submitted in research reports and the Nonclinical Overview and Written Summary in the NDA submission. The following discussion provides a consolidated summary and interpretation of the skin lesions observed in rats and monkeys. In addition, a review of the clinical safety database for pregabalin-treated patients with diabetic peripheral neuropathy (DPN) is included to provide perspective on the clinical relevance of these findings. In the clinical analysis, the COSTART preferred adverse event term of "Healing Abnormal" was investigated.

Intravenous toxicity studies in rats, and monkeys were conducted to support potential parenteral administration of pregabalin, although this route is not under consideration for clinical development. An assessment and discussion of dermatopathy noted in intravenous bolus, and continuous infusion studies in rats and monkeys and an investigative time-course study in monkeys are also included below for informational purposes.

To summarize, in oral nonclinical safety studies in rats and monkeys, the occurrence of dermatopathy was dose-related, was generally localized to the tail, and often resolved despite continued treatment. Furthermore, dermatopathy was generally reversible following drug withdrawal. There is no evidence from nonclinical studies that pregabalin treatment interferes with skin healing following oral or intravenous bolus administration. The etiopathogenesis of skin changes following oral administration is not known. The oral route is the intended route for clinical administration of pregabalin. Administration by continuous infusion to monkeys resulted in widespread subcutaneous edema followed by dermatopathy associated with endothelial injury. Edema was not observed in rats or monkeys following oral administration, suggesting that the pathogenesis for dermatopathy may differ by oral and continuous intravenous administration.

From the available data, Pfizer concludes that the dermatopathy observed in the nonclinical studies does not appear to be relevant to humans given the low incidence of wound-healing abnormalities in the DPN population and in pregabalin-treated patients across all indications, and does not suggest a need for special concern in diabetic patients treated with pregabalin.

## 1. SUMMARY OF DERMATOPATHY IN NONCLINICAL SAFETY STUDIES

Evaluations of tail/skin lesions in rats and monkeys included clinical signs noted in-life and pathologic evaluation of fully developed lesions at necropsy (gross) and microscopically (only gross lesions collected for microscopic evaluation). Skin lesions in monkeys administered pregabalin by continuous infusion were substantially more pronounced, widespread (involving sites beyond the tail), and were associated with extensive subcutaneous swelling and edema. A time course study was conducted for monkeys administered pregabalin by continuous infusion to investigate the etiopathogenesis of pregabalin-induced tissue swelling/edema and skin lesions in monkeys following administration by continuous intravenous infusion. Time course studies were not conducted in rats (oral, intravenous bolus, or continuous intravenous infusion administration) or in monkeys administered pregabalin by oral and intravenous bolus routes.

### 1.1. Pivotal Oral Rat Studies

In general for rats in the oral studies, drug-related dermatopathy was restricted to the tail, occurred at  $\geq 250$  mg/kg, and involved a dose-related proportion of animals (Table 1 to Table 4, Figures F-1 to F-4). Clinical observations indicated tail changes of erythema and sores could progress to tail tip necrosis and missing tail tip at  $\geq 500$  mg/kg. Tail tip necrosis and missing tail tip were low incidence findings at  $\geq 500$  mg/kg, but were dose-related. Most tail lesions in rats  $\leq 1250$  mg/kg healed even with continuous treatment. Healing of tail lesions at  $\leq 1250$  mg/kg also occurred following cessation of treatment (reversal phase) if tail tip loss had not occurred. Single occurrences of dermatopathy (skin sores; 1 of 25 per group) were noted in female rats at 50 and 100 mg/kg in a single oral reproductive toxicology study (Table 5) and in a control female in the 52-week chronic study (Table 4). Dermatopathy occurring in rats at  $\geq 50$  mg/kg or 2 times the mean human exposure at the maximum recommended clinical dose (123  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) was considered potentially treatment related for defining safety margins. However, the low incidence in the treatment groups and the occurrence of dermatopathy in control rats at a similar incidence indicates this safety margin was conservative. Skin changes noted at locations other than tail were rare events and were not considered drug-related. Drug-related effects were not noted on extremities (forelimbs or hindlimbs), and edema was not noted clinically or as a pathological component of tail lesions. To assess a possible contribution of an immunologic component in the pathogenesis of dermatopathy in the rat, the potential for pregabalin to induce contact sensitization (allergic dermatitis) was studied in the local lymph node assay. Pregabalin at 5% and 7.5% topically did not induce contact sensitization in rats (Study AA2650; RR 745-03326).

### 1.2. Intravenous Rat Studies

There were not drug-related tail lesions noted in rats following intravenous bolus administration into the tail vein for up to 4 weeks (Study SP1637; RR 250-01812). Tail changes at injection sites were similar between treated and controls, and were both of low incidence. These sites (tail and tail veins) would have experienced locally high drug concentrations by this route of administration. Thus, it is unlikely that the vascular exposure to high drug concentrations alone can be viewed as the sole precipitating factor for lesion induction. Additionally, the lack of a dose-related response at injection sites on the tail suggests that pregabalin does not have adverse effects on healing of traumatic injury associated with repeated daily venipuncture over a 4-week

study. Dermatopathy was similar in control and treated rats given pregabalin by continuous infusion into jugular veins for up to 2 weeks (Study SP1645; RR 250-01818).

### 1.3. Pivotal Oral Monkey Studies

In monkeys given oral doses of pregabalin, skin changes were sporadic and of limited distribution except at the highest doses (500 mg/kg and 500 mg/kg BID) with AUC(0-24) values  $\geq 990$   $\mu\text{g}\cdot\text{hr}/\text{mL}$  (Table 6 to Table 8, Figures F-5 to F-8). Skin alterations were prominent and common at  $\geq 500$  mg/kg almost exclusively on the tail; one female at 500 mg/kg for 4 weeks also had skin sores on the hindpaws. Tail amputation was necessary in 5 of 30 animals at  $\geq 500$  mg/kg. The occurrence of similar skin changes in several control animals confounded interpretation of drug-related effects at 25 mg/kg. Defining effects at this dose (25 mg/kg) were based largely on the incidence of a clinical finding within the 52-week phase of the chronic study rather than a distinct and striking difference in character of the change. Additionally, tail changes were not noted in the 4-week oral and the 13-week phase of the 52-week study at this dose, and changes in the chronic 52-week study had resolved by study termination. Therefore, effects at 25 mg/kg were considered potentially drug-related and were associated with AUC(0-24) values  $\geq 219$   $\mu\text{g}\cdot\text{hr}/\text{mL}$  or approximately 2 times the mean human exposure at the maximum recommended clinical dose. In the 52-week phase of the chronic study, tail lesions healed clinically by study termination despite continued drug treatment in monkeys at  $\leq 100$  mg/kg and in all but 1 monkey at 500 mg/kg (Animal 1000). In the oral program in monkeys, widespread tissue swelling and edema were not noted in clinical observations or pathologic findings.

To investigate the potential mechanisms of tail dermatopathy, subcutaneous tail temperature, as an indirect measure of tail blood flow, was determined. Measurements were obtained pretest in all animals, and then 2 hours postdose daily during Weeks 2 through 4 in controls and at 250 and 500 mg/kg. There were no consistent differences between control and treated animals, or between affected and unaffected animals within the same dose group.

Anemia and thrombocytopenia, along with the marked agglutination of erythrocytes, were noted in a female at 500 mg/kg at Week 26 (Animal 1000) indicating the possible presence of a cold autoagglutinin. Because cold agglutinins are known to cause agglutination of erythrocytes and vascular obstruction in extremities (Reynaud's phenomenon), it was considered this mechanism might have played a role in the tail dermatopathy that occurred in monkeys in this chronic study. As such, blood smear examinations for erythrocyte autoagglutinins and serum protein electrophoresis for detection of autoagglutinins were performed in Week 35. Slight autoagglutination of erythrocytes occurred in at least 1 animal at each dose except controls, with a higher incidence in animals at 500 mg/kg (Table 8). However, the presence of agglutination in some animals at Week 35 did not correlate well with the presence of tail dermatopathy. In addition, there were no drug-related changes in gamma globulins. Autoagglutination was not apparent in blood smears obtained for routine hematologic analyses at study termination, nor was there histopathologic evidence of vascular obstruction. Therefore, it could not be concluded that a cold agglutinin-induced coagulation disorder was involved in the pathogenesis of skin lesions in monkeys.

#### 1.4. Intravenous Monkey Studies

There were apparent differences in magnitude and nature of skin lesion development based on bolus versus continuous infusion administration in the monkey. Drug-related skin lesions were not apparent in intravenous bolus studies at doses up to 200 mg/kg (AUC(0-24) up to 2180  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) daily for 4 weeks (Study AA2314; RR 745-03033). In contrast, pronounced subcutaneous edema or swelling of abdomen, scrotum, limbs, paws, lips eyelids, and tail were present in monkeys given pregabalin by continuous infusion for 2 weeks at all doses (AUC(0-24) of 343 to 1224  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ); sores and erosions occurred on tail and paws, limbs, and lips of some animals (Study SP1644; RR 250-01817). Vasculopathy characterized by endothelial hypertrophy, thickening of vessel walls, thrombosis, and perivascular inflammatory infiltrates was present in dermal and subcutaneous vessels including capillaries, arterioles, venules, and lymphatics. Vascular necrosis was also present in the more severe skin lesions. Degeneration, vesiculation and/or necrosis with ulceration occurred in the epidermis.

The pathogenesis/time course of tail/skin changes was explored in monkeys administered pregabalin by continuous infusion for up to 96 hours due to the severity of lesions observed by this route/method of administration (Study SP1655; RR 250-01888). This study indicated that edema and endothelial injury preceded dermatopathy. The earliest changes were observed histopathologically and ultrastructurally at 24 hours, but were not manifested grossly until 48 hours or clinically until 72 hours. Vascular lesions and edema preceded the appearance of skin sores, indicating treatment-related vascular changes are central to the etiopathogenesis of pregabalin-induced skin lesions following continuous infusion. There was no evidence of a primary immunologic component to the vascular/tissue injury. The nature of the mixed cell vascular inflammatory response is not typical of the monomorphic cell response expected in immune-mediated dermatitis and the earliest changes were observed by 24 hours of treatment. Further, there was no increase in serum concentrations of specific classes of immunoglobulins. Additionally in the chronic oral study, skin lesions in some monkeys healed despite continued treatment; this healing response would not be expected with an immune mechanism.

#### 1.5. Nonclinical Conclusion

Nonclinical safety studies in rats and monkeys indicate dermatopathy was a dose-related effect, was generally localized to the tail, and often regressed despite continued treatment. Furthermore, dermatopathy was reversible following cessation of treatment. Because of lesion regression with continued treatment and reversibility of the skin changes, there is no evidence that pregabalin treatment hampers skin healing in oral or intravenous bolus studies. The etiopathogenesis of skin changes following oral administration is not known. Oral administration is the intended route of human administration. When pregabalin is administered by continuous infusion to monkeys, widespread subcutaneous edema can occur followed by dermatopathy in association with endothelial injury. As continuous intravenous infusion is not an intended route of pregabalin administration in humans and because edema and dermatopathy associated with endothelial injury are not observed with oral administration, these findings are not considered indicative of human risk.

## 2. SUMMARY OF RELEVANT CLINICAL FINDINGS

A review of the clinical safety database for pregabalin-treated patients with DPN provided perspective on the nonclinical findings. The term "healing abnormal" (COSTART) was reported in 9 of 8666 patients (0.1%) (2.7.4 Appendix ALL.28). Three of these 9 patients were from DPN studies (3 of 1413, 0.2%) (2.7.4 Appendix DPN.31). The investigator terms for the events occurring in the DPN patients were failed left ankle fusion, inflammation wound left leg, and surgical wound of right leg not healed (2.7.4 Appendix ALL.10). One of these DPN patients had a serious adverse event of healing abnormal (Patient 029\_012018 with failed left ankle fusion) (2.7.4 Appendix ALL.62)

Considering the low incidence of wound healing abnormalities in the DPN population and with pregabalin treatment for all indications, it is unlikely that the dermatopathology observed in nonclinical studies is relevant to humans or is cause for special concern in pregabalin-treated patients with diabetes. Consequently, the dermatopathology is not perceived to impact the risk to benefit ratio of pregabalin in the diabetic population.

## 3. OVERALL CONCLUSION

From the available data, Pfizer concludes that the dermatopathy observed in the nonclinical studies does not appear to be relevant to humans given the low incidence of wound healing abnormalities in the DPN population and in pregabalin-treated patients across all indications, and does not suggest a need for special concern in diabetic patients treated with pregabalin.

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**Table 1. Tail Dermatopathy – Rat – 4-Week Oral Study**

Study and RR Number	SP 1554 (RR 250-01722)									
Sex	Males					Females				
Dose	UC	500	1250	2500	5000	UC	500	1250	2500	5000
AUC(0-24) $\mu\text{g}\cdot\text{hr}/\text{mL}$	--	1690	4650	8980	14600	--	1370	3770	8410	11300
Multiple Max Human AUC <sup>a</sup>	--	14	38	73	119	--	11	31	68	92
No. Animals <sup>b</sup>	18	21	21	21	21	18	21	21	21	21
Dermatopathy Total	0	11	17	18	19	0	12	17	12	18
Erythema	--	11	17	17	19	--	10	15	11	16
Skin Missing, Sore, Scab	--	9	15	13	17	--	9	17	7	16
Necrosis	--	1	4	7	13	--	3	5	0	8
Tip Missing	--	--	2	4	3	--	--	7	4	3
Dermatopathy at Week 4	--	0	3	3	5	--	1	6	3	2
Dermatopathy at Week 8	--	0	0	1	1	--	1	2	1	1

<sup>a</sup> Mean human exposure at the maximum recommended clinical dose = 123  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .

<sup>b</sup> Five animals/sex/group remained untreated for an additional 4 weeks to assess reversibility of drug-related effects.

**Table 2. Tail Dermatopathy – Rat – 4-Week Oral Study (Lower Doses)**

Study and RR Number	SP 1566 (RR 250-01730)							
Sex	Males				Females			
Dose	UC	50	100	250	UC	50	100	250
AUC(0-24) $\mu\text{g}\cdot\text{hr}/\text{mL}$	--	181	360	923	--	172	325	729
Multiple Max Human AUC <sup>a</sup>	--	1.5	3.0	8.0	--	1.4	2.6	6.0
No. Animals <sup>b</sup>	18	21	21	21	18	21	21	21
Dermatopathy	0	0	0	9	0	0	0	2
Erythema	--	--	--	3	--	--	--	1
Skin Missing, Sore, Scab	--	--	--	8	--	--	--	2
Necrosis	--	--	--	--	--	--	--	--
Tip Missing	--	--	--	--	--	--	--	--
Dermatopathy at Week 4	--	--	--	4	--	--	--	1
Dermatopathy at Week 8	--	--	--	0	--	--	--	0

<sup>a</sup> Mean human exposure at the maximum recommended clinical dose = 123  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .

<sup>b</sup> Five animals/sex/group remained untreated for an additional 4 weeks to assess reversibility of drug-related effects.

**Table 3. Tail Dermatopathy – Rat – 13-Week Oral Study**

Study and RR Number		AA 1994 (RR 745-02570)									
Sex		Males					Females				
Dose	UC	50	250	500	1250	UC	50	250	500	1250	
AUC(0-24) µg·hr/mL	--	228	1210	2270	5370	--	149	802	1280	4040	
Multiple Max Human AUC <sup>a</sup>	--	1.9	9.8	18	44	--	1.2	6.5	10	33	
No. Animals	10	10	10	10	22	10	10	10	10	22	
Dermatopathy	0	0	1	0	17	0	1 <sup>b</sup>	0	1	10	
Erythema	--	--	1	0	12	--	--	--	1	9	
Skin Missing, Sore, Scab	--	--	--	--	14	--	--	--	1	6	
Necrosis	--	--	--	--	--	--	--	--	0	2	
Tip Missing	--	--	--	--	--	--	--	--	0	1	
Dermatopathy at Week 13	--	--	0	--	0	--	1 <sup>b</sup>	--	0	1	

<sup>a</sup> Mean human exposure at the maximum recommended clinical dose = 123 µg·hr/mL.

<sup>b</sup> Evidence of chewing and not considered drug-related.

**Table 4. Tail Dermatopathy – Rat – 52-Week Chronic Oral Study**

Study and RR Number		AA 1994 (RR 745-02683)							
Sex		Males				Females			
Dose	UC	50	250	500	UC	50	250	500	
No. Animals <sup>a</sup>	25	25	25	25	25	25	25	25	
Dermatopathy	1	0	2	6	1	0	1 <sup>b</sup>	9	
Erythema	--	--	0	1	--	--	--	9	
Skin Missing, Sore, Scab	1	--	2	6	1	--	--	5	
Necrosis	--	--	--	--	--	--	--	--	
Tip Missing	--	--	--	--	--	--	--	--	
Dermatopathy at Week 27	0	--	0	0	0	--	0	0	
Dermatopathy at Week 52	1	--	0	0	0	--	1 <sup>b</sup>	0	

<sup>a</sup> Ten animals/sex/group terminated in Week 27 and 15 animal/sex/group terminated at Week 52.

<sup>b</sup> Evidence of chewing and not considered drug-related.

**Table 5. Tail Dermatopathy – Rat – Pre- and Postnatal Development – Oral Study**

Study and RR Number		AA 1960 (RR 745-02628)					
Sex		Females					
Dose	VC	50	100	250	1250	2500	
AUC(0-24) µg·hr/mL	--	241	601	1380	5760, 6580 <sup>a</sup>	8930 <sup>a</sup>	
Multiple Max Human AUC <sup>b</sup>	--	2.0	4.9	11	50	73	
No. Animals	50	25	25	25	25	25	
Tail Sores	0	1	1	3	4	2	

<sup>a</sup> Individual data.

<sup>b</sup> Mean human exposure at the maximum recommended clinical dose = 123 µg·hr/mL.

**Table 6. Tail Dermatopathy – Monkey – 4-Week Oral Study**

Study and RR Number	AA 1929 (RR 745-02329)											
Sex	Males						Females					
Dose	VC	25	50	100	500	500BID	VC	25	50	100	500	500BID
AUC(0-24) µg hr. mL	--	219	469	421	990	2130	--	230	385	388	1090	1500, 3110 <sup>2</sup>
Multiple Max Human AUC <sup>b</sup>	--	1.8	3.8	3.4	8.0	17	--	1.9	3.1	3.2	8.9	19
No. Animals <sup>c</sup>	8	4	4	4	4	4	8	4	4	4	4	4
Dermatopathy	0	0	0	0	1	2	0	0	0	0	1	1
Skin Sore	--	--	--	--	1	2	--	--	--	--	1	--
Swelling and Amputation	--	--	--	--	--	1	--	--	--	--	--	1
Necrosis	--	--	--	--	--	--	--	--	--	--	1	--
Dermatopathy at Week 4 <sup>d</sup>	--	--	--	--	1	2	--	--	--	--	1	1

<sup>a</sup> Individual values.

<sup>b</sup> Mean human exposure at the maximum recommended clinical dose = 123 µg·hr/mL.

<sup>c</sup> 1 animal/sex/drug-treated group and 2 controls/sex remained untreated for an additional 4 weeks to assess reversibility of drug-related effects.

<sup>d</sup> No animals with tail sores in groups designated for reversal phase.

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**Table 7. Tail Dermatopathy – Monkey – 13-Week Phase of Chronic Oral Study**

Study and RR Number	AA 1992 (RR 745-02559)									
	Males					Females				
Time	VC	10	25	100	500	VC	10	25	100	500
Dose	VC	10	25	100	500	VC	10	25	100	500
AUC(0-24) $\mu\text{g}\cdot\text{hr}/\text{mL}$	--	91.1 <sup>a</sup>	219	421	990	--	91.1 <sup>a</sup>	230	388	1090
Multiple Max Human AUC <sup>b</sup>	--	0.7	1.8	3.4	8.0	--	0.7	1.9	3.2	8.9
No. Animals	4	3	3	3	4	4	3	3	3	4
Dermatopathy – See below	1	0	0	1	4	0	0	0	3	2
Tail Amputation	0	0	0	0	1	0	0	0	0	1

Clinical signs noted for each monkey in the 13-Week Phase of the Chronic Oral Study:

Males

Females

**VC:**

1 with skin sore, Tail, Weeks 3-8

**10 mg/kg:** None

**25 mg/kg:** None

**100 mg/kg:**

1 with Dermatopathy, Tail, Slough skin, fissure, cracks, necrotic tip. Weeks 6-13\*

**500 mg/kg:**

1 with Dermatopathy, Tail, slough skin, erosions distal 1/2, fissures, necrotic tip Weeks 5-13, also Skin Sore, Tail, Week 13, Tail Amputated.

1 with Dermatopathy, Tail, Erosion at tip, slough skin, erosion distal 1/2, erosions entire, necrotic tip. Weeks 4-13\*

1 with Dermatopathy, Tail, slough skin cracks distal 1/2, slough skin 1/2, multiple crusts/erosions. Weeks 4-13\*

1 with Dermatopathy, Tail, fissures, sloughing skin, erosions distal, erosions entire, also Swelling, Tail, at base. Weeks 3-13\*

**VC: None**

**10 mg/kg:** None

**25 mg/kg:** None

**100 mg/kg:**

1 with Dermatopathy, Tail, crusts, also Skin Sore, Tail, ventral tail base. Week 13

1 with Dermatopathy, Tail, Scaly skin, crusts. Weeks 3-13

1 with Dermatopathy, Tail, Multiple erosions, and crusts. Weeks 11-13\*

**500 mg/kg:**

1 with Dermatopathy, Tail, Slough skin, erosions, crusts. Weeks 8-13\*

1 with Dermatopathy, Tail, Distal scaly skin, healing erosions, slough skin, necrotic tip, erosions, Weeks 2-7 also Skin sore, Tail, bilateral at base tail Weeks 9-13, Swelling Week 13\*, stump and at base, Amputated.

\* Indicates clinical sign disappeared prior to the animal's termination.

<sup>a</sup> Calculated combined-sex value; remaining values from 4-week oral repeated-dose toxicity study (AA 1929).

<sup>b</sup> Mean human exposure at the maximum recommended clinical dose = 123  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .

**Table 8. Tail Dermatopathy – Monkey – 52-Week Phase of Chronic Oral Study**

Study and RR Number	AA 1992 (RR 745-02646)									
Sex	Males					Females				
Dose	VC	10	25	100	500 <sup>a</sup>	VC	10	25	100	500 <sup>a</sup>
No. Animals	3	3	3	3	3	3	3	3	3	3
Dermatopathy – See below	2	0	2	0	3	0	2	1	2	3
Tail Amputation	0	0	0	0	1	0	0	0	0	0
Erythrocyte Autoagglutination - Slight	0	1	1	2	2	0	0	0	3	3

Clinical signs noted for each monkey in the 52-Week Phase of the Chronic Oral Study:

Males	Females
<b>VC:</b> 1 with Dermatopathy; Tail, Scaly skin. Weeks 4-8 1 with Skin Sore, Tail, Near tip. Weeks 13-14	<b>VC: None</b>
<b>10 mg/kg: None</b>	<b>10 mg/kg:</b> 1 with Dermatopathy, Tail, Mild app dist 6 inches crusts, mild crusts healing, Weeks 30-39. 1 with Skin Sore Tail, Dorsal, Middle, Middle- healing, Weeks 50-65*
<b>25 mg/kg:</b> 1 with Dermatopathy, Tail, multiple erosions and crusts, crusts, crusts healing, Weeks 13-42, also Erythema, Tail, at base, Weeks 54-55, also Skin Sore, Tail, multiple entire tail, Week 13 1 with Dermatopathy, Tail, Lichenified skin, scaly skin. Weeks 0-8	<b>25 mg/kg:</b> 1 with Dermatopathy, Tail, Crusts, Mild, Weeks 54-57
<b>100 mg/kg: None</b>	<b>100 mg/kg:</b> 1 with Dermatopathy, Tail, Crust at tip, 1 at middle, Middle and crust at tip, lesions healing; Weeks 13-28 1 with Dermatopathy, Tail, Crusts, crusts – healing, Weeks 13-38
<b>500 mg/kg:</b> 1 with Dermatopathy, Tail, Multiple erosions, and crusts, multiple crusts, Weeks 13-22; also Skin Sore Tail, Mid, Weeks 58-61 1 With Dermatopathy, Tail, Slough/crack skin dist., fissures/slough skin, necrotic tip, scaly skin, scaly and scabby skin, Weeks 4-34; also Erythema, Tail, Near tip, Weeks 19-20. Tail Amputated. 1 with Dermatopathy, Tail, erosion tip circum, Weeks 13-22; constriction band at tip, Weeks 22-58.	<b>500 mg/kg:</b> <b>1 with Dermatopathy, Tail, Erosions and crusts, crusts and scales, scales, Weeks 8-65</b> 1 with Dermatopathy, Tail, Crust at tip, tip healing, Weeks 18-30 1 with Dermatopathy, Tail, Erosions, slough skin, crusts, crusts healing, Weeks 8-30

\* Indicates clinical sign disappeared prior to the animal's termination. Bold indicates only animal with tail lesions present to termination.

<sup>a</sup> Animals originally given 250 mg/kg for 13 weeks followed by 500 mg/kg for 52 weeks.

**Table 113. Pregabalin Oral Toxicodynamics**

Significant Effect	Species	No-Effect Dose AUC(0-24)	Lowest-Effect Dose AUC(0-24)
Hypoactivity/ Hyperactivity/Ataxia	Rat	Effects at all doses studied.	50 mg/kg
	Monkey	≤100 mg/kg ≤388 µg·hr/mL	173 µg·hr/mL <sup>a</sup> 500 mg/kg 990 µg·hr/mL
Decreased Platelets	Rat	Effects at all doses studied.	50 mg/kg 228 µg·hr/mL <sup>b</sup>
Dermatopathy	Rat	Effects at all doses studied.	50 mg/kg
	Monkey	10 mg/kg ≤91.1 µg·hr/mL	241 µg·hr/mL <sup>c</sup> 25 mg/kg 219 µg·hr/mL
Nasal Discharge/Rhinitis	Monkey	50 mg/kg ≤385 µg·hr/mL	100 mg/kg 388 µg·hr/mL
Developmental Toxicity Decreased Fetal Weight	Rat	1250 mg/kg ≤6590 µg·hr/mL	~2500 mg/kg ~9470 µg·hr/mL
	Rabbit	500 mg/kg ≤2020 µg·hr/mL	1250 mg/kg 4750 µg·hr/mL
Developmental Toxicity Decreased Offspring Wt	Rat	50 mg/kg ≤241 µg·hr/mL <sup>c</sup>	100 mg/kg 601 µg·hr/mL
	Rat	250 mg/kg ~1320 µg·hr/mL <sup>d</sup>	1250 mg/kg 3320 µg·hr/mL
Prolonged Diestrus, Estrus	Rat	500 mg/kg ≤1020 µg·hr/mL	1250 mg/kg 3340 µg·hr/mL
Dystocia	Rat	250 mg/kg ≤1380 µg·hr/mL <sup>c</sup>	1250 mg/kg 5760 µg·hr/mL <sup>c</sup>
Carcinogenicity - No Drug-Related Tumors	Rat	450 mg/kg (M) ≤1740 µg·hr/mL	900 mg/kg (F) ≤2960 µg·hr/mL
Carcinogenicity- Hemangiosarcomas	Mouse B6C3F1	200 mg/kg ≤153 µg·hr/mL	1000 mg/kg 653 µg·hr/mL
	Mouse CD-1	1000 mg/kg ≤558 µg·hr/mL	5000 mg/kg 3150 µg·hr/mL
Death	Rat	50 mg/kg ≤228 µg·hr/mL <sup>b</sup>	250 mg/kg 802 µg·hr/mL <sup>b</sup>
	Monkey	≤500 mg/kg ≤1090 µg·hr/mL	1000 or 500 BID mg/kg 1100 µg·hr/mL <sup>c</sup>

<sup>a</sup> Value obtained from a supportive toxicokinetic study by gavage.

<sup>b</sup> Value obtained from a 13-week toxicity study by diet.

<sup>c</sup> Value obtained from a prenatal-postnatal study by gavage.

<sup>d</sup> Value approximated from the first male fertility and early embryonic development study by gavage.

<sup>e</sup> Individual animal value.

rats. In a second investigative study in male and female rats given oral doses for 2 weeks, platelet count decreased at  $\geq 500$  mg/kg although not significantly. Template bleeding time, a more accurate procedure, was unaffected up to 2500 mg/kg. A low incidence ( $\leq 5\%$ ) of subtle morphologic platelet abnormalities consisting of giant size, decreased granularity, and/or enlarged granule size occurred at  $\geq 500$  mg/kg, and a mild effect on platelet aggregation was noted at 2500 mg/kg, but reticulated platelet number, activated platelet and clot retraction percentages, and bone marrow megakaryocyte parameters were unchanged. Overall, platelet function in rats appears unaffected by pregabalin up to 2500 mg/kg with AUC(0-24) up to 9170  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .

#### 2.6.6.9.3. Dermatopathy

Skin lesions characterized clinically by a spectrum of lesions ranging from erythema to necrosis, and histopathologically by hyperkeratosis, acanthosis, fibrosis, and/or necrosis of the tail, were observed in rats given  $\geq 50$  mg/kg in oral repeated-dose studies, with associated AUC(0-24)  $\geq 241$   $\mu\text{g}\cdot\text{hr}/\text{mL}$ . Lesions typically appeared within the first 2 weeks of treatment at higher doses and resolved in most affected animals by Week 7 in the 13-week study and by Week 4 in the 52-week study. Similar skin lesions were observed in monkeys in oral repeated-dose studies, and were located primarily on the tail in most animals. In the chronic monkey study, lesions were observed at  $\geq 25$  mg/kg, with plasma pregabalin AUC(0-24) values  $\geq 219$   $\mu\text{g}\cdot\text{hr}/\text{mL}$ . As in rats, lesions in affected animals in the chronic monkey study generally resolved prior to study termination. Subcutaneous tail temperature, used as an indirect measure of tail blood flow in the chronic monkey study, showed no consistent differences between control and high-dose animals, or between affected and unaffected animals within the same group. Pregabalin at 5% and 7.5% did not induce contact sensitization (allergic dermatitis) in rats in the local lymph node assay. The etiology of the skin lesions remains unknown. No tail dermatopathy was observed in mice given repeated oral doses of pregabalin up to 13000 mg/kg up to 13 weeks. Missing tail tips were observed in mice given up to 5000 mg/kg in the B6C3F1 but not the CD-1 carcinogenicity study, however, the relationship of this lesion to dermatopathy in rats and monkeys is unknown.

#### 2.6.6.9.4. Rhinitis

Rhinitis was observed in oral repeated-dose studies in monkeys at  $\geq 100$  mg/kg, with pregabalin AUC(0-24) values  $\geq 388$   $\mu\text{g}\cdot\text{hr}/\text{mL}$ . Nasal discharge in the chronic study, characterized as serous, purulent, or bloody, was not clearly related to drug treatment as it was present pretest in some animals, occurred at all doses including controls, and was generally of short duration and self-limiting. Skin sores in the nostrils were observed in 1 female at 500 mg/kg at a plasma concentration 2 hours postdose in Week 52 of 68.2  $\mu\text{g}/\text{mL}$ .

#### 2.6.6.9.5. Reproductive Toxicity

Effects on reproductive organs were observed in male rats (Table 2.6.7.17D, RR 250-01790).<sup>480</sup> Epididymal enlargement, epididymal tubular hypospermia, and fibrosis and mononuclear cell infiltrates in the interstitium were observed at  $\geq 500$  mg/kg in a 4-week

53 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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Lisa Malandro  
5/26/04 01:12:23 PM



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/s/

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Parinda Jani  
4/16/04 12:36:19 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

APR 15 2004

Dear Mr. [ ]

Between March 1 and 8, 2004, Mr. Thomas W. Nojek, representing the Food and Drug Administration (FDA), conducted an investigation and met with you and members of your staff to review your practices as a Contract Research Organization for the clinical investigation (protocol # 1008-131 entitled: "An 8-Week, Double-Blind, Placebo-Controlled Trial of Pregabalin [300mg/day] for Relief of Pain in Patients With Painful Diabetic Peripheral Neuropathy") of the investigational drug pregabalin, performed for Pfizer, Inc. by [ ]

[ ] This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

We appreciate the cooperation shown Investigator Nojek during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.  
Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-170 Doc.Rm. NDA#21-446

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (Kashoki)

HFD-170 PM (Malandor)

HFD-46/47c/r/s/ GCP File #

HFD-46/47 GCP Reviewer (Currier)

HFD-46/47 CS

HFR-CE450 DIB (Heppe)

HFR-CE450 Bimo Monitor (Cochran)

HFR-CE450 Field Investigator (Nojek)

GCF-1 Seth Ray

r/d: cac:4/12/04

reviewed:KMU:4/12/04

f/t:ml:4/12/04

o:\cac\2004\ — LTR.doc

**Reviewer Note to Rev. Div. M.O.**

DSI routinely inspects the sponsor, monitor, or CRO that performs the monitoring duties in submissions for new molecular entities (NME). — (CRO) monitored the studies for the NME pregabalin, NDA 21-446. The study conducted by Dr. L \_\_\_\_\_ I was selected for coverage. No significant deviations from regulations were noted during the inspection. Monitoring of the study appeared adequate.

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/s/

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Khin U  
5/6/04 08:43:01 AM

**Malandro, Lisa**

CMC- IR

**From:** Malandro, Lisa  
**Sent:** Wednesday, April 14, 2004 11:36 AM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Ware, Jacqueline H  
**Subject:** NDA 21-446, -723, -724, Information Request from CMC

4-14-04

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Jonathan,

The Chemists have requested that you provide the stability data analysis of the dissolution data at 15, 20 and 30 minute time points in SAS transport file format. Please submit your response to this request in electronic archival format as amendments to NDA 21-446, NDA 21-723, NDA 21-724 [ I

Thanks,

Lisa

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/s/

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Lisa Malandro  
4/14/04 11:36:28 AM

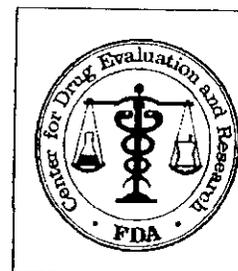
## Industry Meeting Minutes

**Date/Time:** April 13, 2004 / 1:30 pm      **Location:** Parklawn, Conference Room B

**Applications:** NDAs 21-446 (lead), 21-723      J

**Sponsor:** Pfizer, Inc.

**Drug/Dosage Form/Doses:** LYRICA™ (pregabalin) Capsules,  
20/50/75/100/150/200/225/300 mg



**Indication:** Neuropathic pain (diabetic peripheral neuropathy and post-herpetic neuralgia),      J

**Type of Meeting:** Type A meeting to discuss abuse potential of pregabalin

**Meeting Chair:** Deborah B. Leiderman, M.D., Director, Controlled Substance Staff

**Minutes Recorder:** Lisa M. Malandro, Regulatory Project Manager, HFD-170

Sponsor Attendees	Title
Jonathon Parker, RPh, MS	Global Regulatory Leader
Jim Bammert, RPh	US Regulatory Lead
Paul Nitschmann, MD	Global Therapeutic Area Leader - Neurology
Cheryl Graham, MD, FCP	Regulatory Policy
Toni Hoover, PhD	Development Site Head/Ann Arbor
Rich Kavoussi, MD	Global Clinical Leader
Charlie Taylor, PhD	CNS Pharmacology
Len Meltzer, PhD	CNS Pharmacology
Rachel Sobel, MPH	Epidemiology
Kathleen Dowd	Pregabalin US Team Leader - NY
Valerie Flapan, JD	Regulatory Counsel
FDA Attendees	Title
<b>Controlled Substances Staff</b>	
Deborah B. Leiderman, M.D., M.A.	Director
Michael Klein, Ph.D.	Team Leader
Katherine Bonson, Ph.D.	Pharmacologist
Lin-Whei Chuang	Pharmacologist
Office of Drug Evaluation (ODE) II & HFD-170	Title
Bob Meyer, M.D.	Director, ODE II
Lee W. Ripper	Associate Director for Regulatory Affairs, ODE II
Bob Rappaport, M.D.	Director, HFD-170
Rigoberto Roca, M.D.	Deputy Director, HFD-170
Celia Winchell, M.D.	Team Leader, Drug Abuse Products, HFD-170
Parinda Jani	Chief, Project Management Staff, HFD-170
Mwango Kashoki, M.D.	Clinical Reviewer, HFD-170
Lisa M. Malandro	Regulatory Project Manager, HFD-170

**Meeting Objective:** To discuss the preliminary assessment by the Controlled Substance Staff (CSS) that pregabalin be considered for scheduling under the Controlled Substances Act (CSA).

**General Discussion:** Following introductions, Dr. Rappaport stated that representatives of the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170) were in attendance to listen to the discussion regarding abuse potential and to facilitate the meeting, if necessary. Dr. Klein addressed the Sponsor's questions that were included in the April 9, 2004, meeting package. The slide presentation, including the Sponsor's questions and the CSS responses, are presented below in boxes. Discussion is presented in normal text following the slide presentation.

*Slide 1*

**Rates of the COSTART term "euphoria" in GAD trials**

**Question 1:**

*Does the Agency agree that the inconsistent spontaneously reported adverse events of euphoria with pregabalin, that do not recur on re-challenge, are not necessarily predictive of abuse potential, especially in light of the other clinical and nonclinical data available to assess abuse liability?*

*Slide 2*

- No.
- Euphoria was reported in 5 distinct human populations:
  - 3 patient populations in the clinical safety/efficacy studies (GAD, neuropathic pain, epilepsy)
  - a drug abusing population in the human laboratory abuse potential study
  - a healthy subject population in the pharmacokinetic studies
- Monkeys self-administered pregabalin in two preclinical studies.

*Slide 3*

**Clinical Safety/Efficacy Studies**

- Euphoria provides a signal of abuse potential.
- The incidence of "euphoria" as an adverse event in the pregabalin clinical trials was as follows:

*Slide 4***Incidence of Euphoria in Clinical Trials with Pregabalin**

<u>Pregabalin Dose</u>	<u>GAD</u>	<u>Epilepsy</u>	<u>Neuropathic Pain</u>
150 mg	0.5%	0	1.0%
<b>200 mg</b>	<b>10.3%</b>		
300 mg	3.3%	2.2%	2.4%
<b>400 mg</b>	<b>4.8%</b>		
<b>450 mg</b>	<b>11.8%</b>		
600 mg	2.5%	1.0%	1.5%
all doses	4.5%	0.8%	1.4%
placebo	1.2%	0.3%	0

*Slide 5*

- The rate of euphoria reported in pregabalin clinical trials is high and extremely unusual. The rate of euphoria, as noted by Sponsor, in bupropion clinical trials was less than 1 percent.

(Ref: Wellbutrin and Zyban labels)

*Slide 6***Human Laboratory Abuse Potential Study**

- Pregabalin was tested in sedative/alcohol-abusing individuals.
- Subjective assessments of "good drug effect", "high", "liking" and "liking (end of session)" in response to the 200 and 450 mg doses of pregabalin were similar to or greater than the responses to 15 and 30 mg of diazepam, a Schedule IV drug of abuse.
- These data strongly suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam.

*Slide 7***Human Pharmacokinetic Studies**

- In the pharmacokinetic studies, 43 of 440 healthy subjects (9.8%) experienced "euphoria" (28 mild, 14 moderate, 1 severe) in response to pregabalin.
- Euphoria reports in the pharmacokinetic studies are very unusual.

Slide 8

**Preclinical Studies**

- Monkeys self-administered pregabalin in 2 separate studies for several days at a rate equal to or greater than 10 injections/day, demonstrating that pregabalin is sufficiently reinforcing for animals to work to obtain it. These observations indicate that humans are likely to experience the drug as reinforcing.

Slide 9

**Question 2:**

*Since the adverse event of euphoria is not reliably associated with abuse liability in other marketed drugs, what is the relevance of this spontaneously reported adverse event in determining risk for drug abuse?*

Slide 10

- The consistent finding of high rates of euphoria in 3 clinical populations, as well as in the human laboratory study and the pharmacokinetic studies, strongly suggests that pregabalin exerts psychic effects that humans find pleasurable and hence is likely to be abused.
- The adverse event profile provides part of the evidence but is not relied upon in isolation from other data.
- The established human laboratory abuse potential method, which demonstrated that pregabalin produced effects similar to those of diazepam (Schedule IV in the Controlled Substances Act), provides strong evidence for abuse potential.

Slide 11

**Subjective response of "good drug effect", "high", "liking", and "liking (end of session)" in the human abuse potential study (Study 098)**

**Question 3:**

*Does the Agency agree that the pregabalin findings of drug liking could reflect false-positive results and therefore do not reflect abuse potential sufficient to warrant scheduling?*

Slide 12

- False positives are always theoretically possible. However, the concordance of the multiple sources of data make it unlikely.
- The reliability of the euphoric response across different clinical populations suggests that this effect is not a false-positive.
- The Sponsor may further explore pregabalin's abuse potential by designing a placebo-controlled human laboratory abuse potential study that compares pregabalin to a known drug of abuse (positive control), and to a drug without demonstrated abuse liability that mimic some of the effects.
- CSS is available to review protocol proposals.

Slide 13

**Self-Administration of Pregabalin by Primates:**

**Question 4:** *Does the Agency agree that maintenance of self-administration behavior is critical to identifying positive reinforcing effects indicative of abuse liability?*

**Question 5:** *Does the Agency agree that the sporadic and transient self-administration responses obtained with pregabalin in primates (similar to vehicle) do not constitute a signal for reinforcing effects?*

Slide 14

- We view the self-administration study as a predictor of human abuse if animals find a drug to be reinforcing following acute administration.
- There are too many methodological issues with the conduct of the studies to allow for further interpretation.
- Monkeys self-administered pregabalin for several days at a rate equal to or greater than 10 injections/day (standard in this paradigm), demonstrating that they experience pregabalin as sufficiently reinforcing to work to obtain it.

Slide 15

- Several methodological issues in the Sponsor's primate studies preclude reaching any conclusions about the maintenance of chronic reinforcing effects.
- In general, a faster infusion rate of a psychically reinforcing drug produces greater reinforcing responses.
- The infusion rates in the two pregabalin self-administration studies varied greatly.

*Slide 16*

- Monkeys self-administered pregabalin despite the fact that it was infused over a 25 sec period, compared to the 5 sec infusion for methohexital (the positive control) or placebo. The methohexital infusion rate was 5 times faster than that of pregabalin, which makes comparisons between the self-administration rates of these two drugs difficult.
- In the pregabalin vs. pentobarbital self-administration study, the infusion rate was based on body weight, which varied between animals. Thus, comparisons between drug groups, and between animals in the same drug group, are problematic.

*Slide 17*

- Most important, the monkey self-administration findings are consistent with the human laboratory study that found pregabalin to be as reinforcing as diazepam.

*Slide 18*

**Key Comments on Eight Factor Analysis**

**Question 6:**

*Does the Agency agree that the extensive gabapentin data provide a useful benchmark for assessing the abuse potential of pregabalin?*

No

Gabapentin and pregabalin differ in their chemistry, pharmacology, and toxicological profiles.

*Slide 19*

**Question 7:**

*Does the Agency agree with our conclusion that we have provided sufficient data to support the lack of scheduling for pregabalin?*

*Slide 20*

- No. As already discussed, the presence of euphoria following pregabalin administration in 5 human populations (3 patient populations, a drug abusing population, and healthy subjects) demonstrates that pregabalin produces reinforcing responses.
- According to the legislative history of the CSA, a new drug has a potential for abuse if it is related in action to a drug or drugs already listed in the CSA, to make it likely that the new drug will have the same potential for abuse as the known drugs.
- Pregabalin subjective responses were similar to those of diazepam (a Schedule IV drug in the CSA) in a human abuse potential study where subjects reported that pregabalin induced a "good drug effect", "drug liking," and production of a "high".

*Slide 21*

**Question 8:**

*Is the Agency agreeable to a meeting with Pfizer, the reviewing Divisions, CSS and NIDA to discuss the complete 8-factor assessment of pregabalin?*

*Slide 22*

- We always welcome the submission of additional data. Today's meeting addresses the Sponsor's questions.
- Under the CSA, the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (DHHS) has the authority and responsibility to conduct a medical and scientific analysis of available data to assess whether a drug has abuse potential. This authority is further delegated to the FDA.

*Slide 23*

- Based on the medical and scientific assessment, an Eight Factor Analysis is prepared by FDA, with concurrence of NIDA, that is sent for signature by ASH at DHHS. The recommendation and Eight Factor Analysis are then sent to the DEA.
- DHHS and its agencies do not consult with drug sponsors during the drug scheduling process. However, in the case of new drugs in development, we rely on the data submitted by the Sponsor to prepare the Eight Factor Analysis.

April 13, 2004

## DISCUSSION:

The Sponsor stated that pregabalin is similar in structure and chemistry to gabapentin and that post-marketing experience has not revealed that Neurontin is an abused substance. They added that CSS has primarily considered the similarities between pregabalin and diazepam. However, pregabalin is not pharmacologically similar to benzodiazepines or to other drugs with known abuse potential. Unlike benzodiazepines, pregabalin does not bind to either GABA- or benzodiazepine-receptors, nor does pregabalin alter brain GABA concentrations. Also, in animal studies, pregabalin has not been recognized as being similar to benzodiazepines. The Sponsor questioned if the pharmacological similarities between gabapentin and pregabalin, and the dissimilarities between benzodiazepines and pregabalin, had been considered during the CSS abuse liability review.

Dr. Leiderman stated that neither pharmacological nor chemical similarity between pregabalin and benzodiazepines is required to support a recommendation for scheduling. The Controlled Substances Act specifies effects similar to known drugs of abuse. The finding from the pregabalin human abuse potential study that experienced substance abusers had a similar response to pregabalin as they did to diazepam is therefore more relevant than any pharmacological similarity, or lack thereof, of pregabalin to benzodiazepines.

The Sponsor stated that similar sites of action are required for a pharmacological effect, and that the similarities between gabapentin and pregabalin are therefore relevant. The Sponsor expressed their belief that the post-marketing data supporting a lack of abuse of gabapentin should be taken into account because of the pharmacologic similarities between gabapentin and pregabalin. Dr. Leiderman noted that the Sponsor did not provide any studies comparing the abuse potential of gabapentin to pregabalin. Dr. Bonson added that, if the Sponsor had provided data that compared the abuse potential of gabapentin and pregabalin directly, these data would have been considered. The CSS staff is mandated to evaluate the data that they receive and to make a decision based on that information. CSS will always evaluate new data that are submitted and reassess its conclusion if warranted.

The Sponsor remarked that pharmacological comparisons of drugs are routinely performed. Dr. Leiderman replied that pregabalin as a NME must be evaluated as a unique drug. Furthermore, there are clear differences between pregabalin and gabapentin in other areas, such as toxicology. The Sponsor requested further discussion with the CSS staff to discuss various study designs to assess the abuse liability of the drug.

The Sponsor described the relapse prevention study in patients with Generalized Anxiety Disorder (GAD) in which patients who reported euphoria upon initial dosing did not report this effect upon readministration of pregabalin. The Sponsor stated that they believe that this study shows that pregabalin does not show positive reinforcing effects. Dr. Leiderman observed that CSS had not seen any data with respect to duration of AEs, such as euphoria.

The Sponsor also noted that their contention is further supported by the pre-clinical acute-administration study in which the animals did not self-administer pregabalin for the duration of the study. In a nonclinical study of methohexital in primates, there was no difference in self-administration between pregabalin and saline. The Sponsor added that saline was also self-administered. Dr. Bonson replied that these findings suggest that this study was invalid. According to the Sponsor, in a study of pentobarbital and pregabalin that adhered to Good Laboratory Practices (GLP), it was concluded that pregabalin was not a positive reinforcer because there was a low FRI.

April 13, 2004

Dr. Leiderman stated that, if the pre-clinical data showed positive reinforcement of pregabalin, but these observations were not seen in human studies, then the abuse potential would be of less concern. Alternatively, if the animal data were equivocal or open to interpretation, and were unaccompanied by any signal from the human studies, we would likely dismiss the animal findings. However, this is not the case: In addition to the non-clinical data, there is a signal in clinical populations. Dr. Bonson clarified that the CSS evaluates acute self-administration response in animal studies. Data from the acute self-administration studies are relevant because substance abusers tend to abuse drugs on an intermittent basis. Dr. Bonson stated one monkey self-administered more than ten times during the study.

The Sponsor stated that the time to effect in the human abuse potential study was longer than one would expect for abusers in a population with a history of drug abuse. In this study, pregabalin produced a high score on the "sedation" scale. Dr. Klein stated that there were too many outcome variables in the protocol, which allowed for manipulation of endpoints to support many hypotheses. CSS noted the protocol was not submitted to CSS for review prior to conduct of the study.

The Sponsor asked what steps they could take following this meeting. They asked if it were possible to respond to the points brought up during the discussion. Also, since it appeared that Dr. Bonson had several questions regarding some of the studies presented in the application, could the CSS staff provide a list of questions that the Sponsor can address? Dr. Leiderman stated that the data will determine the decision regarding scheduling of pregabalin. She suggested that the Sponsor further evaluate the data already available regarding patient reports of euphoria to determine factors such as severity, duration, and onset. However, she noted that the degree of concordance and consistency across human populations and in the pre-clinical data is very unusual for a drug product. Dr. Leiderman stated that new pre-clinical studies that address the previous studies' methodological concerns are probably indicated. In the future, the CSS staff would like to see formal studies of the psychic effects of pregabalin.

The Sponsor asked if it was possible for them to receive a copy of the Eight Factor Analysis that the CSS staff was preparing for the Drug Enforcement Administration (DEA). Dr. Leiderman stated that this was not possible due to the CSA requirements. A scheduling determination must be made by the Assistant Secretary for Health (ASH) to the DEA. The DEA ultimately publishes a final determination. The Sponsor asked if it was possible to provide a response to the CSS comments made during this meeting prior to the completion of the "Eight Factor Analysis." The CSS staff stated that this is an ongoing process and they would review and consider any comments, documentation, etc. during their review. They also reminded the Sponsor that, if the drug is approved under NDA regulations, they have agreed not to market until the scheduling process has been completed.

The Sponsor stated that there is an additional clinical study that may influence a scheduling determination. Dr. Leiderman stated that the study would be considered along with those already reviewed. The Sponsor asked whether, if the study's findings of likeability are similar to those previously discussed, CSS would still recommend scheduling. Dr. Leiderman stated that these data would be evaluated in conjunction with the data that have already been submitted and reviewed by the Agency. The Sponsor asked how they would know when CSS would complete the "Eight Factor Analysis." Dr. Leiderman said that it is a lengthy process involving CDER, the FDA Office of the Commissioner, the Department of Health and Human Services (DHHS) as well as DEA. She assured the Sponsor that CDER will keep them advised of where they are in the scheduling process.

April 13, 2004

The meeting adjourned at 2:30 pm

Minutes prepared by:

Lisa M. Malandro

*[See appended electronic signature page]*

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Minutes concurred by Chair:

Deborah B. Leiderman, M.D., M.A.

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/s/

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Parinda Jani  
5/17/04 08:41:50 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

APR 13 2004

Joseph S. Gimbel, M.D.  
2525 West Greenway Road, Suite 114  
Phoenix, Arizona 85023

Dear Dr. Gimbel:

Between March 2 and 5, 2004, Mr. Armando Chavez, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # 1008-131 entitled: "An 8-Week, Double-Blind, Placebo-Controlled Trial of Pregabalin (300 mg/day) for Relief of Pain in Patients with Painful Diabetic Neuropathy") of the investigational drug Lyrica (pregabalin), performed for Pfizer Research and Development. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigation. We are aware that at the conclusion of the inspection, Mr. Chavez presented and discussed with you and Mr. Dellario, Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not conduct the clinical investigations according to the investigational plan [21CFR 312.60].

- a. The protocol requires that subjects with a creatinine clearance of  $\leq 60$  mL/min be excluded from the study. However, subject 113001 was enrolled into the study with a baseline creatinine clearance value of 55 mL/min.
- b. The protocol listed benzodiazepines as prohibited concomitant medications and required a 7-day washout period prior to study entry. However, subject 113017 was taking a benzodiazepine before and during the study.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 2 - Joseph S. Gimbel, M.D

We appreciate the cooperation shown Investigator Chavez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Khin Maung U, M.D.  
Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

Page 3 - Joseph S. Gimbel, M.D

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

Deficiencies noted:

failure to adhere to protocol (05)

cc:

HFA-224  
HFD-170 Doc.Rm. NDA# 21,446  
HFD-170 Review Div.Dir. (Rappaport)  
HFD-170 MO (Kashoki)  
HFD-170 PM (Malandro)  
HFD-46/47c/r/s/ GCP File #  
HFD-46/47 GCP Reviewer (Currier)  
HFD-46/47 CS  
HFR-PA252 DIB (Maxwell)  
HFR-PA2565 Bimo Monitor (Koller)  
HFR-PA 2540 Field Investigator (Chavez)  
GCF-1 Seth Ray

r/d: Currier:4/1/04  
reviewed:KMU:4/7/04  
f/t:sg: 4/8/04

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**Reviewer Note to Rev. Div. M.O.**

This inspection was issued as a routine PDUFA assignment. Dr. Gimbel's study was identified as one of the important studies supporting NDA 21-446.

Source documents, case report forms (CRFs), subject diaries, clinical charts, lab testing records, drug accountability records, IRB documentation, and correspondence files for two protocols were examined during the inspection. For protocol 1008-131, 23 subjects were screened, 7 subjects failed screening, 12 subjects enrolled. All 12 subjects completed the study. Study

Page 4 - Joseph S. Gimbel, M.D

records for all 12 subjects were reviewed in depth. Consent forms for all subjects were verified as present and properly signed. All primary efficacy endpoints were properly recorded, and all AEs were properly reported to the sponsor and the IRB.

The inspection revealed 2 protocol deviations:

- 1) One subject was entered with a creatinine clearance of 55 mL/min, whereas the protocol required > 60mL/min. (A 24-hour urine creatinine clearance could be used for subjects that did not have 60 mL/min from the blood creatinine clearance test, but there were no records that a urine test was done.) The subject was ineligible for the study.
- 2) One subject took Estazolam before and during the trial. Benzodiazepines were prohibited by the protocol. The subject completed the trial using the prohibited med.

The two subjects were ineligible to enter the study. We recommend that you review the data from subjects 113001 and 113017 to determine if the above protocol deviations would require the removal of their data from efficacy analysis.

With those exceptions, the (remaining) data from Dr. Gimbel's study could be used to support an approval decision for the NDA.

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/s/

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Khin U

4/13/04 04:56:18 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

April 8 2004

Albert J. Tamoush, M.D.  
Neurologist  
Drexel University College of Medicine  
245 South Broad Street, MS 423  
Philadelphia, Pennsylvania 19102

Dear Dr. Tamoush:

Between March 15 and 22, 2004, Mr. Mike M. Rashti, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # 1008-014 entitled: "A Double-Blind Placebo-controlled Trial of Pregabalin for the Treatment of Painful Diabetic Neuropathy") of the investigational drug pregabalin, performed for Pfizer Global Research and Development. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

We appreciate the cooperation shown Investigator Rashti during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.  
Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

CFN/FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD- 170 Doc.Rm. NDA# 21-446

HFD- 170 Review Div.Dir. (Rappaport)

HFD- 170 MO (Hashoki)

HFD- 170 PM (Malandro)

HFD-46/47c/r/s/ GCP File # 11155

HFD-46/47 GCP Reviewer (Carrier)

HFD-46/47 CS

HFR- CE150 DIB (Baker)

HFR- CE1515 Bimo Monitor (Tammarielo)

HFR- CE150 Field Investigator

GCF-1 Seth Ray

r/d: cac:3/30/04

reviewed:KMU:3/30/04

f/t: sg:4/1/04

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**Reviewer Note to Rev. Div. M.O.**

This was a routine PDUFA clinical investigator inspection issued per program plans. Dr. Tamoush's site was identified as one of five important studies supporting NDA 21-446. The study covered by inspection was protocol 1008-014, entitled: "A Double-Blind Placebo-controlled Trial of Pregabalin for the Treatment of Painful Diabetic Neuropathy". The study was sponsored by Pfizer Global Research and Development. This was the first inspection of Dr. Tahmoush. Dr. Tahmoush served as both principal investigator and research coordinator for the study.

Twenty-four subjects were screened for this study; 15 were entered. There were no dropouts and all 15 were considered evaluable. There were no deaths in the study and only 1 SAE, which was appropriately reported to the sponsor and the IRB. The FDA field investigator examined all 24 study files for the presence of signed consent forms; all were present. Source documents, including study records, lab results, and ECGs, were checked against case report forms (CRFs) and data listings sent by the sponsor to FDA, for 8 subjects. There were no data discrepancies. All AEs were reported, all inclusion/exclusion criteria were followed, there was evidence of adequate monitoring, and drug accountability was reconcilable. There were no deviations from FDA regulations found during the inspection. From the information inspected, the data from Dr. Tahmoush's study could be used to support an approval decision for the NDA.

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/s/  
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Khin U  
4/14/04 04:42:04 PM



Food and Drug Administration  
Rockville MD 20857

APR - 8 2004

Alfredo L. Jacome, M.D.  
Renstar Medical Research  
2121 S.W. 22<sup>nd</sup> Place  
Ocala, Florida 34474

Dear Dr. Jacome:

Between March 3 and 12, 2004, Ms. Madelyn Renteria, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of two clinical investigations:

Protocol 1008-029 entitled: "A 5-Week, Double-Blind, Placebo-Controlled Trial of 3 Dosages of Pregabalin [75, 300 & 600 mg/day] for Treatment of Patients with Painful Diabetic Peripheral Neuropathy", and

Protocol 1008-131 entitled: "An 8-Week, Double-Blind, Placebo-Controlled Trial of Pregabalin [300 mg/day] for Relief of Pain in Patients With Painful Diabetic Neuropathy", performed for Pfizer Global Research and Development.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Renteria presented and discussed with you and members of your staff, Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct the clinical investigations according to the investigational plans [21CFR 312.60].
  - a. Protocol 1008-029 required that the site call each study subject twice during the titration period (one week), and once during each subsequent week until the termination visit. Telephone Contact Worksheets show that subjects 001, 004, 005, 013, 014, 017, 019, and 024 did not receive two calls during the titration period and subjects 005, 014, 017, 019,

024, 023, 030, and 035 did not receive subsequent calls at the required intervals. Protocol 1008-131 required that the site call the study subject at least once between each study visit from visit 2 until the termination visit. Subject 122010 did not receive phone calls at the required intervals.

- b. For protocol 1008-029, laboratory tests and procedures were not performed according to the protocol:
  - 1) For subject 013, the hematology lab was not performed on visit 3.
  - 2) For subject 017, the SF-36 Quality of Life questionnaire was completed at visit 1 instead of visit 2.
  - 3) For subject 021, Hemoglobin A1C and Study Medication Plasma concentration tests were not done on visit 5.
  - 4) For subject 023, an ECG was not done on visit 5.
2. You did not maintain adequate records of the disposition of the study drug [21 CFR 312.62(a)].

For protocol 1008-029, drug receipt documents indicate that the site received a total of 256 containers of study drug. Records of drug used and drug returned to the sponsor account for 244 containers. In addition, drug re-order forms were present for 18 subjects, yet there is no record of additional drug shipped or used.

3. You did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].

For protocol 1008-029, the data on source documents did not match data on case report forms (CRFs).

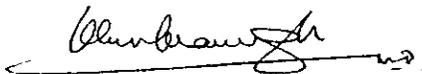
- a. For subject 004, source documents for visit 5 do not list the subject's weight whereas the CRF lists the weight as 100kg.
- b. For subject 023, the source document for visit 3 lists the standing blood pressure (BP) as 122/82, whereas the CRF lists the standing BP as 132/82.
- c. For subject 039, there was no source document for the physical exam vitals at visit 3, although vitals are recorded on the CRF.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 3 – Alfredo I. Jacome, M.D.

We appreciate the cooperation shown Investigator Renteria during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

A handwritten signature in cursive script, appearing to read "Khin Maung U", with a horizontal line underneath it.

Khin Maung U, M.D.  
Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

Page 4 – Alfredo I. Jacome, M.D.

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- VAI 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

- inadequate drug accountability (04)
- failure to adhere to protocol (05)
- inadequate and inaccurate records (06)

cc:

HFA-224  
HFD-170 Doc.Rm. NDA#21-446  
HFD-170 Review Div.Dir. (Rappaport)  
HFD-170 MO (Hashoki)  
HFD-170 PM (Malandro)  
HFD-46/47c/r/s/ GCP File #11149  
HFD-46/47 GCP Reviewer (Currier)  
HFD-46/47 CS  
HFR-SE250 DIB (Gallant)  
HFR-SE250 Bimo Monitor (Torres)  
HFR-SE250 Field Investigator (Renteria)  
GCF-1 Seth Ray

r/d: cac:3/25/04:3/28/04  
reviewed:KMU:3/29/04  
f/t:ml/sg:4/1/04

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**Reviewer Note to Rev. Div. M.O.**

This inspection was issued as a routine PDUFA assignment. Dr. Jacome's study was identified as one of the important studies supporting NDA 21-446.

Source documents, case report forms (CRFs), subject diaries, clinical charts, lab testing records, drug accountability records, IRB documentation, and correspondence files for two protocols were examined during the inspection. For protocol 1008-029, 39 subjects were screened, 13 subjects failed screening, 26 subjects enrolled. All 26 subjects completed the study. Study

Page 5 – Alfredo I. Jacome, M.D.

records for 17 of the 26 subjects were reviewed in depth. For protocol 1008-131, 18 subjects were screened, 7 subjects failed screening and 11 subjects enrolled. All 11 subjects completed the study. Study records for all 11 subjects were reviewed in depth. Consent forms for all subjects in both protocols were verified as present and properly signed. All primary efficacy endpoints were properly recorded, and all AEs were properly reported to the sponsor and the IRB.

The inspection revealed instances of protocol deviations, inaccurate record-keeping, and inadequate drug accountability. Protocol deviations included the failure to contact subjects within the time intervals specified by the protocol, and failure to perform a few of the required labs and tests for a few of the subjects. Data recorded in source documentation did not match data recorded in a few subjects' CRFs, however, the missing or inaccurate data appears to be due to clerical and transcription errors. Twelve bottles of study drug were unaccounted for (256 bottles shipped to the site, 244 bottles used or returned to the sponsor). The site had no explanation for the discrepancy.

Although the deficiencies noted during the inspection were numerous, none were serious or repeated. It appears that the protocol deviations, data errors, and drug accountability problems would not impact on the outcome of the study treatment on the subjects or impact the integrity of the study as a whole. From the records inspected, the data from Dr. Jacome's study could be used to support an approval decision for the NDA.

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/s/

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Khin U  
4/14/04 04:45:43 PM

Malandro, Lisa

Clinical IR

4-1-04

**From:** Malandro, Lisa  
**Sent:** Thursday, April 01, 2004 4:12 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Malandro, Lisa  
**Subject:** NDA 21-446 Request for Information--clinical

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Jonathan,

The Medical Officer has requested the following information. Please provide written response as soon as possible. The action date is drawing near...

- How many investigators (principal and sub-investigators) participated in (a) DPN and (b) PHN trials?
- Of the 187 investigators from whom financial disclosure information was not obtained, how many participated in (a) DPN and (b) PHN trials?
- The integrated safety database does not include data from Phase 2/3 trials conducted in Japan. Provide your rationale for excluding data from these patients from the integrated safety database.

Thanks,  
Lisa

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/s,

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Lisa Malandro  
4/6/04 10:55:50 AM



NDA 21-446, 21-723

Pfizer Global Research & Development  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

LSS  
DISCIPLINE REVIEW LETTER

3/25/04

Attention: Jonathon Parker, R.Ph., M.S.  
Director, Worldwide Regulatory Affairs

Dear Mr. Parker:

Please refer to your October 30, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lyrica™ (pregabalin) Capsules 25, 50, 75, 100, 150, 200, 225, and 300 mg.

We also refer to your submission dated January 30, 2004.

We have received the following comments from the Controlled Substance Staff (CSS, HFD-009) in response to our consult request.

Based upon review of all the data provided in your application, CSS concludes that pregabalin has an abuse liability similar to that of diazepam, a Schedule IV substance under the Controlled Substance Act (CSA).

As required by the CSA (21 USC 811(c)), CSS is preparing an "Eight Factor Analysis", a document that evaluates pregabalin in terms of its potential for abuse. In this document, CSS will recommend that pregabalin be placed into Schedule IV of the CSA. The "Eight Factor Analysis" is transmitted to the Drug Enforcement Administration (DEA) under the signature of the Assistant Secretary for Health at the Department of Health and Human Services, with the concurrence of the FDA Commissioner and the National Institute on Drug Abuse.

The most salient findings for this conclusion are that pregabalin produced a high rate of euphoria (4.8-11.8%) relative to placebo (1.2%) in general anxiety disorder (GAD) clinical trials. This strongly suggests that pregabalin has reinforcing properties.

Additionally, in the clinical abuse potential study, conducted in sedative/alcohol-abusing subjects, subjective responses to "good drug effect", "high", "liking" and "liking (end of session)" for the 200 and 450 mg doses of pregabalin were similar to or greater than the responses to 15 and 30 mg of diazepam. These data strongly

suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam.

Finally, pregabalin produced self-administration in rhesus monkeys at the 3.2 and 10 mg/kg infusion doses during initial access to the drug. This also demonstrates that the drug produces reinforcing effects.

In submitting the NDA application, you have agreed to not market the drug product, if FDA determined that the drug should be scheduled under the CSA, until the DEA has issued a final schedule ruling. FDA/CDER has initiated the drug scheduling process and has notified the DEA. However, you should be aware that scheduling actions by the DEA involve several federal agencies and multiple clearances, and therefore, can take an unpredictable period of time before finalization occurs.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Parinda Jani  
3/25/04 01:51:55 PM

CSS Consult/Review  
3/31/04

MEMORANDUM  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
CONTROLLED SUBSTANCE STAFF

---

**Date:** March 24, 2004

**To:** Bob Rappaport, M.D., Director  
Division of Anesthetics, Critical Care and Addiction Drug Products  
(HFD-170)

**Through:** Deborah B. Leiderman, M.D., Director  
Michael Klein, Ph.D., Team Leader  
Controlled Substance Staff (HFD-009)

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff (HFD-009)

**Subject:** Consult on abuse potential for NDA review  
NDA 21-446, 21-723, 21-724 [ ]  
Lyrica (pregabalin)  
Treatment for (respectively) neuropathic pain associated with  
diabetes, neuropathic pain associated with herpes zoster,  
epilepsy [ ]  
Sponsor: Pfizer, Inc.

**Background:**

The Division of Anesthetics, Critical Care and Addiction Drug Products (HFD-170) consulted CSS regarding the abuse potential of pregabalin (Lyrica). Pregabalin is a calcium channel blocker at the alpha-2-delta protein subunit that is being developed for the treatment of neuropathic pain associated with diabetes, neuropathic pain associated with herpes zoster, epilepsy [ ] Some of the medications approved for the treatment of pain and GAD are controlled substances under the Controlled Substances Act (CSA). The Sponsor proposes that pregabalin not be controlled under the CSA, citing the results from non-clinical studies, clinical trials and human abuse potential studies as support for their position that pregabalin lacks abuse potential and should be approved for marketing as a non-scheduled drug.

**Conclusions and Recommendations:**

Based upon review of all the data provided by the Sponsor, CSS concludes that pregabalin has an abuse liability similar to that of diazepam, a Schedule IV substance under the CSA.

As required by the CSA (21 USC 811(c)), CSS is preparing an "Eight Factor Analysis", a document that evaluates pregabalin in terms of its potential for abuse. In this document, CSS will recommend that pregabalin be placed into Schedule IV of the CSA. The "Eight Factor Analysis" is transmitted to the Drug Enforcement Administration (DEA) under the signature of the Assistant Secretary for Health at the Department of Health and Human Services, with the concurrence of the FDA Commissioner and the National Institute on Drug Abuse.

The most salient findings for this conclusion are that pregabalin produced a high rate of euphoria (4.8-11.8%) relative to placebo (1.2%) in GAD clinical trials. This strongly suggests that pregabalin has reinforcing properties.

Additionally, in the clinical abuse potential study, conducted in sedative/alcohol-abusing subjects, subjective responses to "good drug effect", "high", "liking" and "liking (end of session)" for the 200 and 450 mg doses of pregabalin were similar to or greater than the responses to 15 and 30 mg of diazepam. These data strongly suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam.

Finally, pregabalin produced self-administration in rhesus monkeys at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug. This also demonstrates that the drug produces reinforcing effects.

In submitting the NDA application, the Sponsor agreed to not market the drug product, if FDA determined that the drug should be scheduled under the CSA, until the DEA has issued a final schedule ruling. FDA/CDER has initiated the drug scheduling process and has notified the DEA. However, the Sponsor and HFD-170 should be aware that scheduling actions by the DEA involve several federal agencies and multiple clearances, and therefore can take an unpredictable period of time before finalization occurs.

## I. Summary of Data Related to Abuse Potential from Clinical Studies

### A. Clinical Studies Assessing Safety and Efficacy of Pregabalin

#### *Incidence of "Euphoria"*

A high rate of euphoria was reported by Generalized Anxiety Disorder (GAD) patients taking pregabalin in clinical trials: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. In contrast, the placebo-treated rate of euphoria in GAD patients was 1.2%. No GAD patients who experienced euphoria had a history of drug or alcohol abuse. Since drugs are scheduled on the basis of behavioral effects suggestive of abuse potential, not on therapeutic indication, the presence of a high rate of euphoria in any clinical population suggests a safety issue with pregabalin.

In addition, the reported incidence of euphoria from pregabalin was 1.0-2.4% in neuropathic pain patients and 1.0-2.2% epilepsy patients, at doses of 150, 300 and 600 mg,

relative to the incidence in the placebo-treated groups (0.0% in neuropathic pain patients and 0.3% in epilepsy patients). It is noteworthy that the doses used in the GAD clinical trials that produced euphoria (200, 400 and 450 mg) were not tested in the neuropathic pain and epilepsy clinical trials. It is possible that the 200, 400 and 450 mg doses would produce euphoria if they were administered to other patient populations.

Additionally, in the clinical pharmacology (pharmacokinetic) studies, 43 of 440 healthy subjects (9.8%) experienced "euphoria" (28 mild, 14 moderate, 1 severe).

#### *Physical Dependence and Withdrawal Syndrome*

When discontinuation-emergent symptoms are summed across short-term psychiatric studies with pregabalin at doses ranging from 150-600 mg/day, the most frequently observed adverse events compared to placebo were insomnia, headache, nausea, infection and diarrhea.

When a similar evaluation was conducted for long-term psychiatric studies with pregabalin, the rate for adverse events in pregabalin-treated subjects was greater than that seen in placebo-treated subjects for insomnia, nausea, headache, diarrhea and chills. These data are suggestive of the presence of a withdrawal syndrome in psychiatric patients, indicative of physical dependence.

In contrast, the rate of adverse events during discontinuation from pregabalin in the neuropathic pain study was similar to that of placebo.

An evaluation of the psychiatric studies using the Physician's Withdrawal Checklist showed significant differences in withdrawal scores between pregabalin and placebo. The withdrawal symptoms were experienced by patients at all doses of pregabalin, although not every dose of pregabalin showed significant differences from placebo in every psychiatric study.

A post-hoc analysis of two pharmacokinetic studies in which pregabalin was administered for either 2 or 4 weeks showed that the rate of discontinuation-emergent signs and symptoms was similar to placebo, although the profile was different. In the 2-week study, healthy volunteers received either placebo or a single pregabalin dose of 25-300 mg on Days 1 and 22 and multiple doses of 75, 300, 600 or 900 mg/day on Days 8-21. In the 4-week study, healthy volunteers received either placebo or 900 mg/day of pregabalin on Days 1-28 and a single 300 mg dose of pregabalin on Day 29. Pregabalin discontinuation produced such symptoms as headache, nausea and diarrhea, while placebo discontinuation produced accidental injury, infection, skin disorder and ventricular extrasystoles.

## **B. Clinical Abuse Potential Studies**

In the clinical abuse potential study, subjective responses to "good drug effect", "high" "liking" and "liking (end of session)" for the 200 and 450 mg doses of pregabalin were similar to or greater than the those for 15 and 30 mg of diazepam. Subjects identified the 200 mg dose of pregabalin as a sedative while identifying the 450 mg dose as a sedative/stimulant. These data suggest that the abuse potential of pregabalin is similar to or greater than that of diazepam, a Schedule IV drug. It is notable that the majority of subjects were alcohol users, with only a few subjects who were users of sedatives and/or sedatives plus alcohol. This suggests that individuals without sedative abuse histories may experience pregabalin as reinforcing.

## **C. Psychomotor Clinical Studies**

In three separate clinical abuse potential studies, subacute administration of pregabalin was synergistic with oxycodone, lorazepam and ethanol in producing performance deficits in psychomotor tasks. In a separate clinical abuse potential study, subacute administration of pregabalin (alone) produced a similar degree of performance deficits in psychomotor tasks as alprazolam (alone).

## **II. Summary of Data Related to Abuse Potential from Preclinical Studies**

### **A. Receptor Binding**

Pregabalin does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the calcium channel. This is similar to the binding profile for gabapentin. The mechanism of action of pregabalin is not well understood.

### **B. Microdialysis in Rats**

Morphine increased extracellular levels of dopamine in the nucleus accumbens, but pregabalin and saline did not. Pregabalin blocked the increase in dopamine following morphine administration. Since dopamine levels are increased by many, but not all, drugs of abuse, this suggests that pregabalin does not have the same reinforcing effects as morphine, as Schedule II drug.

### **C. Behavioral Studies**

The preclinical behavioral studies with pregabalin are not valid for assessing abuse potential. Deficits in the studies include:

- \* the use of different infusion rates in the methohexital-pregabalin and the pentobarbital-pregabalin self-administration studies, which can affect the apparent reinforcing properties of a drug (ie: faster infusion rates are more reinforcing)
- \* the use of different routes of administration for midazolam and pregabalin in the conditioned place preference study, which can affect the apparent reinforcing properties of a drug (ie: routes with fast onset are more reinforcing)
- \* the 5 hour time lag between drug training and saline training in the conditioned place preference study with rats may be inadequate, since monkeys in a separate study showed behavioral effects for longer than 5 hours after pregabalin administration
- \* the lack of data regarding the pharmacokinetics of pregabalin in animals, which will influence the choice of appropriate pretreatment times
- \* the lack of data regarding the plasma levels of pregabalin produced by the animal doses selected compared to those produced by proposed therapeutic doses

Despite inadequately designed preclinical studies, there are indications in the preclinical studies that pregabalin has abuse potential:

- \* pregabalin produced self-administration of >10 injections/day at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug, thus demonstrating that pregabalin produces reinforcing effects.

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**APPENDIX A:**  
**ABUSE POTENTIAL STUDIES WITH PREGABALIN**

**A. Clinical studies assessing safety and efficacy of pregabalin:**

- \* euphoria
- \* physical dependence/withdrawal

**B. Clinical abuse potential studies with pregabalin:**

- \* clinical abuse liability study
- \* comparison to oxycodone for pharmacokinetics
- \* comparison to lorazepam in psychomotor tasks
- \* comparison to ethanol in psychomotor tasks
- \* comparison to alprazolam in psychomotor tasks

**C. Summaries of preclinical studies:**

- \* receptor binding
- \* in vivo microdialysis in rats
- \* behavioral studies:
  - self-administration
  - conditioned place preference
  - drug discrimination
  - spontaneous behavior
  - locomotor behavior
  - physical dependence/withdrawal

Attachment A:  
CSS Review of Pregabalin Pharmacology

Study Summaries:

A. Clinical Studies Assessing Safety and Efficacy of Pregabalin

Pregabalin has been tested up to 15,000 mg (15 gm) in clinical trials. This is 150-300 times the proposed therapeutic dose of 75 mg BID (oral) for neuropathic pain and epilepsy, and 100 mg BID (oral) for generalized anxiety disorder. Of particular interest is that the Sponsor states that adverse events were not clinically different from those at therapeutically recommended doses.

*Incidence of "Euphoria"*

In the Phase 2/3 studies (controlled and uncontrolled), a total of 423 of 8666 (4.8%) subjects experienced "euphoria" (263 mild, 146 moderate, 14 severe). Twenty-six subjects withdrew due to euphoria. None of the patients who experienced euphoria had a history of drug abuse or dependence. The average time to onset of euphoria was 1 day and duration was 7 days. Euphoria ceased while patients were still taking medication. This suggests that tolerance developed to euphoria during chronic administration. However, a week-long duration of euphoria can be considered a safety and abuse liability issue.

As depicted in **Table 1** (below), a high rate of euphoria was reported by Generalized Anxiety Disorder (GAD) patients taking pregabalin in clinical trials: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. No GAD patients who experienced euphoria had a history of drug or alcohol abuse. Drugs are scheduled on the basis of abuse potential, not on therapeutic indication. The presence of a high rate of euphoria in any clinical population is suggestive of an abuse potential in the general population.

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**TABLE 1****Incidence of Euphoria in Clinical Trials (as reported in proposed label):**

Pregabalin Dose	Incidence of Reports of "Euphoria"		
	GAD	Epilepsy	Neuropathic Pain
150 mg	0.5%	0	1.0%
<b>200 mg</b>	<b>10.3%</b>		
300 mg	3.3%	2.2%	2.4%
<b>400 mg</b>	<b>4.8%</b>		
<b>450 mg</b>	<b>11.8%</b>		
600 mg	2.5%	1.0%	1.5%
all doses	4.5%	0.8%	1.4%
placebo	1.2%	0.3%	0

In contrast to GAD patients, the reported euphoria in the neuropathic pain and epilepsy clinical trials was never above 2.4%. However, the doses that produced euphoria in the GAD clinical trials were not tested in the clinical trials for these indications. This leaves open the possibility that these doses may produce euphoria if they are used in neuropathic pain or epilepsy patients.

In the clinical pharmacology (pharmacokinetic) studies, 43 of 440 subjects (9.8%) experienced "euphoria" (28 mild, 14 moderate, 1 severe).

*Physical Dependence and Withdrawal Syndrome*

When discontinuation-emergent symptoms are summed across short-term psychiatric studies (testing GAD, social phobia, panic disorder and acute mania) with pregabalin at doses ranging from 150-600 mg/day (n = 1851), the most frequently seen adverse events were insomnia (2.4%), headache (2.1%), nausea (1.8%), infection (1.7%) and diarrhea (1.4%). At the 300 mg dose, there was a higher incidence of insomnia (4.1%) and at the 200 mg dose, there was a higher incidence of headache (4.3%). The incidence in placebo-treated subjects (n = 817) was less than 1.5% for these symptoms.

When a similar evaluation was conducted for long-term psychiatric studies with pregabalin at 450 mg/day, the rate for adverse events in pregabalin-treated subjects (n = 429) was greater than that seen in placebo-treated subjects (n = 243): insomnia (5.2% vs. 0.8%), nausea (4.0% vs. 0.8%), headache (3.2% vs. 2.5%), diarrhea (2.8% vs. 0.8%) and chills (2.0% vs. 0.0%). These data demonstrate the presence of a withdrawal syndrome in psychiatric patients, indicative of physical dependence.

In contrast, the rate of adverse events during discontinuation from pregabalin in the neuropathic pain study was less than 1.0% for all symptoms.

An evaluation of the psychiatric studies using the Physician's Withdrawal Checklist showed significant differences in withdrawal scores between pregabalin and placebo. The withdrawal symptoms were experienced by patients at all doses of pregabalin, although not every dose of pregabalin showed significant differences from placebo in every psychiatric study.

A post-hoc analysis of two pharmacokinetic studies in which pregabalin was administered for either 2 or 4 weeks showed that the rate of discontinuation-emergent signs and symptoms was similar to placebo, although the profile was different. In the 2-week study, healthy volunteers received either placebo or a single pregabalin dose of 25-300 mg on Days 1 and 22 and multiple doses of 75, 300, 600 or 900 mg/day on Days 8-21. In the 4-week study, healthy volunteers received either placebo or 900 mg/day of pregabalin on Days 1-28 and a single 300 mg dose of pregabalin on Day 29. Pregabalin discontinuation produced such symptoms as headache, nausea and diarrhea, while placebo discontinuation produced accidental injury, infection, skin disorder and ventricular extrasystoles.

## **B. Clinical Abuse Potential Studies**

### ***Subjective Response Study***

#1008-098

**Abuse liability of pregabalin in recreational sedative/alcohol users**  
(Study conducted by     )

1

This is a crossover study in which subjects were randomized to one of five treatment sequences that included pregabalin (200 and 450 mg), diazepam (15 and 30 mg) and placebo. All study medication was given orally in a total of six capsules per session. Each treatment session was separated by a washout period of at least 5 days.

Fifteen subjects completed the study. All subjects were recreational sedative users (experienced with sedatives at least six times in lifetime) or moderate alcohol users (12 drinks per week for the past year). Ten subjects met alcohol criteria, two met sedative criteria and three met both criteria. Inclusion of volunteers with different drug histories may be inappropriate, since social drinkers and those who use sedatives for non-medical reasons may not have the same subjective responses to sedative administration. Exclusionary criteria included dependence on any drug except for nicotine.

Unusually, the investigators do not have a concluding statement concerning the abuse potential of pregabalin, based on the present clinical abuse potential study.

### Physiological Measures

The only physiological measure that was responsive to drug administration was an increase in heart rate in the diazepam 30 mg group. The Sponsor attributes this to subjects falling asleep and then being startled when awakened for hourly assessments.

Subjective Measures (D = diazepam, P = pregabalin, PL = placebo; dose as number)

A variety of subjective measures from the POMS, ARCI and VAS were collected. Those specifically related to abuse potential assessment are presented below in **Table 2**:

### TABLE 2

#### Comparison of Subjective Response to Pregabalin and Diazepam

(D = diazepam, P = pregabalin, PL = placebo; dose as number)

**Good Drug Effects (VAS)** -- increased by D30 > **P450** > **P200** > D15

**High (VAS)** -- increased by D30 = **P450** > D15 = **P200**

**Liking (VAS)** -- increased by D30 = D15 = **P450** = **P200**

**Liking (End of Session)** -- **P450** > D30 = D15 = **P200**

These data show that both doses of pregabalin produce good effects, high, and drug liking that are equivalent to or greater than at least one dose of diazepam. Notably, the 450 mg dose of pregabalin was liked in the end of session questionnaire better than either dose of diazepam or the lower dose of pregabalin. Since diazepam is a known drug of abuse, these results suggest that pregabalin has similar abuse potential to diazepam.

The data in **Table 3** (below) show that both drugs at the doses tested produce effects that are recognized as sedative effects by subjects. Of interest is that the 450 mg dose of pregabalin is recognized as a both a sedative and stimulant by subjects both during the study (VAS questionnaire) and after the study (Drug Identification Question). However, the ARCI subscale for stimulants (BG scale) did not register this dose of pregabalin as a stimulant.

**TABLE 3**

**Drug Identification Question (End of Session):**

	<u>Placebo</u>	<u>Sedative</u>	<u>Stimulant</u>
Placebo	73%	20%	7%
D15	40%	53%	7%
D30	0	87%	13%
P200	0	73%	27%
P450	20%	40%	40%

**Sedated (VAS) -- increased by D30 > D15 = P200 > P450**

**Stimulated (VAS) -- increased by P450**

**Stimulant-Like (BG Scale of ARCI) -- no change from any drug**

**Multiple Choice Procedure:**

The Sponsor notes that this procedure was developed to assess reinforcing effects with results that are similar to self-administration procedures. Previously, benzodiazepines have been shown to have higher crossover points than placebo. However, in the present study, there were no significant drug effects.

The Sponsor states that, "Individuals tended to always choose drug when the alternative was the loss of money, but they chose money even at the lowest level. Although the cross-over value was lower for placebo (\$0.10) than the drug conditions (all averaged around \$1) these differences were not significant." The Sponsor acknowledges that it is unexpected that diazepam did not produce crossover effects, but does not provide any explanation.

*Studies Investigating Effect of Pregabalin on Task Performance*

#1008-078

**Evaluation of potential pharmacodynamic interaction between pregabalin and oxycodone administered orally to healthy volunteers**

(Study conducted by  $\square$

$\square$

This is a randomized, partial double-blind crossover study. Each of 12 subjects received all four treatments, in randomized order. Subjects did not have experience with drugs of abuse. There were seven days between the start of each treatment phase. The four oral treatments include:

- 1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with 10 mg oxycodone
- 2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with placebo
- 3) placebo every 12 hrs for three doses -- third dose is given with 10 mg oxycodone
- 4) placebo every 12 hrs for three doses -- third dose is given with placebo

Pregabalin was in capsules with matching placebos, but that oxycodone was in tablets that did not match either the pregabalin or the oxycodone placebo tablets. This accounts for the "partial double-blind" statement about design.

Blood was drawn for PK measurements at appropriate times. Oxycodone did not interfere with pregabalin pharmacokinetics. There was no clinically significant reduction in respiration rate or tidal volume from pregabalin alone or with oxycodone.

The pregabalin side effect profile alone included sleepiness, dizziness and asthenia. These effects increased slightly with oxycodone in combination with pregabalin.

A variety of psychomotor tasks were used in this study, including: simple reaction time, choice reaction time, digit vigilance, numeric working memory, immediate word recall, delayed word recall, word recognition, picture recognition, tracking, critical flicker fusion, body sway, and self-rated alertness.

Pregabalin increased reaction times for almost all tests and increased time for task completion. Oxycodone alone did not reduce task performance. The combination of oxycodone and pregabalin produced similar decrements, but these were of greater magnitude than pregabalin alone. However, pregabalin did improve task performance on two tests: improving accuracy on choice reaction time and tracking.

#1008-076

**Evaluation of potential pharmacodynamic interactions between pregabalin and lorazepam administered orally to healthy volunteers**

This is a randomized, double-blind, placebo-controlled crossover study in 12 healthy volunteers. Treatments were given orally, 7 days apart and included:

- 1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with 1 mg lorazepam
- 2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given with placebo
- 3) placebo every 12 hrs for three doses -- third dose is given with 1 mg lorazepam
- 4) placebo every 12 hrs for three doses -- third dose is given with placebo

Blood was drawn for PK measurements at appropriate times. Lorazepam did not interfere with pregabalin pharmacokinetics, and pregabalin did not alter lorazepam pharmacokinetics. There was no clinical significant reduction in respiration rate or tidal volume from pregabalin alone or with lorazepam.

Dizziness, nausea and headache were reported more frequently after subjects received pregabalin with lorazepam than from pregabalin alone.

A variety of psychomotor tasks were used in this study, including: word recognition, immediate word recall, delayed word recall, simple reaction time, choice reaction time, digit vigilance, numeric working memory, picture recognition, visual tracking, critical flicker fusion, body sway, and Bond-Lader VAS.

Pregabalin alone reduced task performance in simple and choice reaction times, working memory, word recall, tracking, body sway and self-rated alertness. Lorazepam alone produced a greater degree of interference with performance than pregabalin on most tasks. The combination of pregabalin and lorazepam produced deficits in task performance that appeared to be synergistic in response, rather than additive. Reaction times, performance speed and sway were especially affected by the drug combination.

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#1008-079

**Double-blind crossover study to evaluate potential pharmacodynamic interactions between pregabalin and ethanol administered orally to healthy volunteers**

(Study conducted by [

]

This is a randomized, double-blind, placebo-controlled crossover study in 11 healthy volunteers. Note that the main question was how pregabalin changes ethanol responses, rather than the other way around. Treatments were given orally, 7 days apart and included:

- 1) 300 mg pregabalin every 12 hrs for three doses -- third dose is given 30 min prior to 0.7 g/kg ethanol
- 2) 300 mg pregabalin every 12 hrs for three doses -- third dose is given 30 min prior to placebo-equivalent ethanol (0.4%)
- 3) placebo every 12 hrs for three doses -- third dose is given 30 min prior to 0.7 g/kg ethanol
- 4) placebo every 12 hrs for three doses -- third dose is given 30 min prior to placebo-equivalent ethanol (0.4%)

Blood was drawn for PK measurements at appropriate times. Ethanol did not interfere with pregabalin pharmacokinetics, nor did pregabalin interfere with ethanol pharmacokinetics. There was no clinically significant reduction in respiration rate or tidal volume from pregabalin alone or with ethanol.

Dizziness, nausea and headache were reported more frequently after subjects received pregabalin with ethanol than from pregabalin alone.

A variety of psychomotor tasks were used in this study, including: word recognition, immediate word recall, delayed word recall, simple reaction time, choice reaction time, digit vigilance, numeric working memory, picture recognition, visual tracking, critical flicker fusion, body sway, and Bond-Lader VAS.

The combination of pregabalin and ethanol prolonged reaction time for simple reaction time and choice reaction time tasks and increased body sway. For all other tasks, pregabalin did not alter the effects from ethanol alone. Interestingly, pregabalin reduced the detrimental effects of ethanol on: accuracy in choice reaction time, speed of digit vigilance, accuracy of immediate word recall and alertness.

Pregabalin alone had no significant effects on task performance. The Sponsor acknowledges this is different than results from other cognitive studies with pregabalin, but provides no explanation. The results are indeed unusual, given that the same dose of pregabalin in other abuse liability studies did produce detriments in task performance.

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#1008-097

**Investigation into the effects of pregabalin, alprazolam and placebo on cognitive and psychomotor function, car driving ability and sleep**

(Study conducted  $\square$

J

This is a randomized, double-blind, 3-way crossover study with treatments administered three times a day (TID). Drug treatments were: pregabalin 150 mg (450 mg/day; 75 mg capsules used), alprazolam 1 mg (3 mg/day; 0.5 mg capsules used), and placebo, with seven day washout inbetween treatments. In each treatment period, subjects were treated for three days, followed by placebo on Day 4.

There were a total of 24 subjects, with 8 subjects each randomized to each of three treatment sequences. Subjects were excluded if they had "clinically significant use of psychotropic medication in the last 3 months".

Critical Flicker Fusion --  $P = A > PL$  -- shows impairment of information processing

Hick's Choice Reaction Time --  $A > P = PL$  -- A impaired motor, recognition and total reaction time.

Compensatory Tracking Task --  $A > P > PL$  -- sensory motor coordination impaired by A more than by P

Line Analog Rating Scale --  $A > P > PL$  on sedation;  $A = P > PL$  for uncoordination; no significant effects in anxiety or depression

Rapid Visual Information Processing --  $A > P = PL$

Sternberg Memory Scanning Task --  $A > P > PL$  -- no serious memory impairment

Leeds Sleep Evaluation Questionnaire --  $A = P > PL$  -- good sleep on both

Sleep EEG --  $P > PL > A$  -- P increased slow wave sleep, A decreased it; overall sleep parameters were improved by both

Wrist Actigraphy -- no difference

Brake Reaction Time --  $A > P > PL$

Side Effect Profile: P produced dizziness, headache, sleepiness. A produced sleepiness, abnormal gait and asthenia.

**Conclusion:** Pregabalin produces mild impairments in motor behavior and information processing

### **C. Summaries of Preclinical Studies**

#### **Receptor Binding Studies**

The Sponsor submitted two charts with  $K_i$  (inhibitory constant) values for various binding sites in the brain.

The first chart compared  $K_i$  values between pregabalin and gabapentin for GABA sites, opioid sites, dopamine transporter, NMDA sites, 5HT1 and 5HT2 sites. Neither drug

produced Ki values in the nanomolar range for any site except for the gabapentin binding site.

The second chart presented Ki values for a full binding profile of CNS neurotransmitter sites. The only sites that showed Ki values in the nanomolar range were the "gabapentin site", commonly known as alpha2-delta1 and alpha2-delta2 sites of the calcium channel.

These data demonstrate that pregabalin does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the calcium channel.

#### *In Vivo Microdialysis with Rats*

Summary data were submitted. Microdialysis was conducted in rat brains, with cannulae extended into the nucleus accumbens for detection of dopamine. Rats were injected (s.c.) with saline, morphine (0.75 mg/kg), pregabalin (10 mg/kg) or a combination of morphine and pregabalin (no doses given), with pregabalin administered 40 min before the morphine.

Morphine significantly increased extracellular levels of dopamine in the nucleus accumbens over an 80 min collection period. Pregabalin and saline had no effect on dopamine. Pretreatment with pregabalin blocked the increase in dopamine levels following morphine administration.

#### *Behavioral Studies with Animals*

No information is provided by the Sponsor concerning the plasma levels of pregabalin produced by the animal doses selected compared to the plasma levels of pregabalin produced by proposed therapeutic doses in humans.

Thus, it is impossible to evaluate the validity of the animal studies in terms of abuse potential of pregabalin.

#### *Self-Administration (Pregabalin vs. Methohexital)*

Monkeys (n = 4) were used in the study, but only 3 of the animals received each dose of the drug. The fourth animal was unable to receive the highest dose because of solubility problems, given that this was the largest monkey of the group.

Monkeys were trained to receive IV injections of methohexital (0.1 mg/kg/injection), following the presentation of a red light and 10 bar presses by the monkey. Monkeys were then offered pregabalin at 1.0, 3.2, 10 and 18 mg/kg/injection. No information is

provided to justify the doses of drugs selected. All experimental sessions lasted 130 min (2 hr, 10 min).

The Sponsor notes that because of the solubility problems with pregabalin, the drug had to be infused over a 25 sec period. However, the methohexital and saline were infused over a 5 sec period. The narrative states that methohexital and saline were also made available in a 25 sec infusion rate, but no data are presented with this designation. It is well known that infusion rate can have a critical impact on the reinforcing effects of a drug, with slower infusions producing lesser reinforcing effects. Thus, comparisons between methohexital given at an infusion rate 5 times faster than that of pregabalin are not valid.

In the summary of abuse potential data, but not in the study summary itself, the Sponsor states that "positive reinforcement" was defined as 10 inj/day for 7 days. This definition is not included in the study summary itself. This may be because the 3.2 mg/kg/infusion produced 14 injections/day and 10 mg/kg/infusion produced 11 injections/day, indicating that these two doses produced positive reinforcement.

The Sponsor notes that evaluation of individual rate data (not submitted) showed that monkeys had a high rate of self-administration of pregabalin during initial exposure to the drug that then declined with further drug availability.

In the conclusion, the Sponsor states that pregabalin produces an inverted U-shaped curve, which is characteristic of drugs of abuse. But the Sponsor interprets this as meaningless since the methohexital self-administration was greater than pregabalin. However, comparisons are not valid between the drug conditions because of the difference in infusion rates. It is clear from the data in this study that pregabalin is self-administered by monkeys, at a rate greater than the 10 injections/day criteria for reinforcement, indicating that pregabalin may have abuse potential.

The Sponsor concludes that pregabalin has "no reinforcing effects" at doses of 1-18 mg/kg/infusion. However, individual and mean data show that animals do self-administer pregabalin above the 10 injections/day criteria set for a reinforcing response during the first week. The Sponsor emphasizes that this self-administration diminished the following week, but this does not obviate the interpretation that pregabalin is reinforcing during initial exposure to the drug.

Given that there is no information submitted in the NDA concerning the development of tolerance with pregabalin, it is possible that tolerance to pregabalin can account for the reduction in self-administration during the second week of access to the drug.

	methohexital	saline	pregabalin (mg/kg)			
	0.1 mg/kg		1	3.2	10	18
Mean	65 + 9	7 + 1	5 + 1	14 + 2	11 + 3	7 + 3

### Self-Administration (Pregabalin vs. Pentobarbital)

Monkeys (n = 4) who had previously been trained to self-administer drugs of abuse, including pentobarbital, were used in the study. Monkeys first received IV saline, and when daily injections were 10 or less, the animals received IV injections of pentobarbital (1.0 mg/kg/injection) until the daily intake was 16 injections per day. Saline was then offered for several days until daily injections returned to 10 or less. Monkeys were then offered pregabalin at 1, 2, 4, and 8 mg/kg/injection. Note that these doses are less than the doses of pregabalin (1.0, 3.2, 10 and 18 mg/kg/injection) used in the self-administration study with methohexital. No information is provided to justify the doses of drugs selected, nor why these differ from the methohexital study. All experimental sessions lasted for 24 hr, compared to the 130 min (2 hr, 10 min) sessions used in the methohexital study. Positive reinforcement was defined as 10 injections/day or greater.

Pentobarbital, pregabalin and saline were infused at a rate of 1 ml/23 sec, with an injection volume of 0.25 ml/kg. No information is provided about the weight of each animal. Thus, it is likely that each monkey received session drugs under varying infusion rates that could be up to or greater than one minute in duration. It is well known that infusion rate can have a critical impact on the reinforcing effects of a drug, with slower infusions producing lesser reinforcing effects. Thus, although there is equivalence in infusion rate between drug conditions for each animal, comparisons of group means from each drug condition are not valid.

The Sponsor concludes that pregabalin has "no reinforcing effects" at doses of 1-8 mg/kg/infusion. However, individual and mean data show that animals do self-administer pregabalin above the 10 injections/day criteria set for a reinforcing response during the first week. The Sponsor emphasizes that this self-administration diminished the following week, but this does not obviate the interpretation that pregabalin is reinforcing during initial exposure to the drug. Given that there is no information submitted in the NDA concerning the development of tolerance with pregabalin, it is possible that tolerance to pregabalin can account for the reduction in self-administration during the second week of access to the drug.

### Conditioned place preference

#### *Study 1*

Rats were tested to see if morphine (0.1, 0.3, 1.0, 2.0 and 3.0 mg/kg, s.c.) or pregabalin (3, 10, 30 mg/kg, p.o.) induced a conditioned place preference (CPP). The results suggest that morphine induced CPP at all but the lowest dose, but that no dose of pregabalin induced a CPP.

### *Study 2*

Pregabalin was tested for its ability to block the development of CPP with morphine. Rats received either pregabalin (1, 3, 10, 30 mg/kg, p.o.) or saline 60 min prior to administration of a submaximal dose of morphine (0.75 mg/kg, s.c.). The 10 mg/kg dose of pregabalin was found to block the development of CPP from morphine.

### *Study 3*

CPP was established in rats with morphine. Pregabalin (10 mg/kg, p.o.) was given 60 min prior to testing to see if it would influence morphine-induced CPP. Pregabalin blocked the maintenance of morphine CPP. Rats were re-tested without further pregabalin administration on the following two days, but morphine CPP returned in the absence of further pregabalin administration.

There are many flaws in the CPP studies. The routes of administration are different between the two drug conditions. It is very unusual to use oral dosing with CPP, and its use makes comparison between the two drug conditions invalid since morphine was administered subcutaneously. The pretreatment time is not given in one study. The separation time between training sessions with drug or saline was only 5 hours. This may not be adequate, given that the behavioral effects of pregabalin were present in monkeys past the 5 hour mark.

## Drug discrimination

### *Study 1*

Monkeys (n = 4) were trained to discriminate 0.56 mg/kg midazolam (s.c., pretreatment time not given) under a stimulus-shock termination schedule. Challenge sessions with pregabalin (30, 100, 180, 300 mg/kg) were conducted with the drug administered orally 4 hr prior to placement in the test cage. All doses of pregabalin were indistinguishable from saline (ie: percent responding on the midazolam lever of less than 7%).

### *Study 2*

Monkeys (n = 3) were treated daily with a combination of diazepam (5.6 mg/kg, p.o., administered 3 hr prior to session) and flumazenil (0.32 mg/kg, s.c., administered immediately prior to session). Thus, the discriminative cue is the effect of flumazenil in producing a benzodiazepine withdrawal syndrome. Monkeys were then tested with pregabalin (30, 100, 180 mg/kg, p.o., administered 4 hr prior to the session) and flumazenil (0.00032 - 0.32 mg/kg, s.c., administered immediately prior to session).

A dose of 0.01 and 0.032 mg/kg of flumazenil in placebo-treated monkeys produced full generalization to the flumazenil cue in diazepam-dependent monkeys. No data are shown from the diazepam/flumazenil trials for comparison. The results with pregabalin-treated

animals showed that pregabalin/flumazenil could produce full generalization to the flumazenil cue, although the dose of flumazenil necessary to produce this effect was larger than that at the 300 mg dose of pregabalin compared to placebo treatment. This indicates that pregabalin does not prevent the development of benzodiazepine withdrawal.

The Sponsor interprets this as indicating that "pregabalin might attenuate some aspects of benzodiazepine withdrawal" but the data do not support this contention.

There are many flaws in the drug discrimination studies. No data are shown from the diazepam/flumazenil trials for comparison. The routes of administration are different in some studies, and the pretreatment times are different in other studies.

### *Study 3*

A published paper was submitted from a study where rats were trained to discriminate morphine (30 mg/kg, s.c., 30 min pretreatment). Gabapentin (1-100 mg/kg, s.c.) did not generalize to morphine and instead generalized to the saline cue. No data are shown in the paper to support this.

### Spontaneous behavior in monkeys

Monkeys (n = 6) received IV pregabalin at doses of 4, 16, 32 and 64 mg/kg. The volume of injection was 0.24, 0.8, 1.6, and 3.2 ml/kg (respectively). Since the infusion rate was 1 ml/23 sec, the speed of injection for the lowest dose was significantly different from that of the highest dose. Animals were observed for 5 hr after pregabalin administration.

The Sponsor notes that animals manifested gross behavioral signs 5 hr after administration of the drug, so for the two final sessions, animals were observed for 24 hr. Since doses of the drug were administered on a randomized basis, not all animals were observed for 24 hr for each dose. Raters were blind to the drug condition in each session.

No gross behavioral changes were seen at 4 mg/kg and retching was seen in one monkey at 16 mg/kg. Two monkeys exhibited tremors at 32 mg/kg. At 64 mg/kg, 3 of 4 monkeys showed slowed motion, ataxia and 2 of 4 animals showed hypoactivity, asthenic posture, frequent drinking, sitting position with fixed eyeball movement, grasping movements. Some of these behaviors were present after 5 hr.

### Locomotor behavior in rats

Pregabalin (3, 10, 30 mg/kg, i.p.), gabapentin (10, 30, 56, 100 mg/kg, i.p.) or saline was administered to rats 45 min prior to administration of cocaine (10 mg/kg, i.p.), amphetamine (0.5 mg/kg, i.p.) or saline. Locomotor behavior was measured in a  $\zeta$  chamber.

The locomotion induced by cocaine was blocked by all doses (10-100 mg/kg) of gabapentin but only at the 30 mg/kg dose of pregabalin. The locomotion induced by amphetamine was blocked by the highest doses of gabapentin (56 mg/kg) and pregabalin (30 mg/kg).

#### Physical Dependence / Withdrawal

Rats received pregabalin (100-400 mg/kg, i.p.) or pentobarbital (up to 900 mg/kg, i.p.) for 12 days. The doses chosen were based on minimum effective dose 40 times that for anxiolysis/analgesia.

The withdrawal signs that were counted included changes in body weight and hyperexcitability. Weight loss during drug discontinuation showed a 3% loss in placebo group, a 14% loss in the pentobarbital group, at a 10-11% loss in the pregabalin group.

Another measure was "cumulative signs in 96 hr", with the vehicle group showing a score of 1, the pentobarbital group at score of 14, and the pregabalin group a score of 4-6.

These data show a mild withdrawal syndrome following discontinuation of pregabalin.

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/s/

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Katherine Bonson  
3/31/04 11:19:58 AM  
PHARMACOLOGIST

Michael Klein  
3/31/04 11:26:33 AM  
CHEMIST

Deborah Leiderman  
3/31/04 11:44:20 AM  
MEDICAL OFFICER

**Malandro, Lisa**

*Clinical IR*  
*3/24/04*

**From:** Malandro, Lisa  
**Sent:** Wednesday, March 24, 2004 10:32 AM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Clinical Information Request

**Importance:** High

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Hi Jonathan,

In the attached Word document, please find several additional requests from the Medical Officer related to the ongoing review of the pregabalin applications. Please submit response to these requests in electronic archival format as amendments to NDA 21-446, NDA 21-723, NDA 21-724, **3**

Please do not hesitate to contact me if I can be of assistance.

Thanks,

Lisa



MO IR  
achment.doc (47 KI

Information request:

1. You have already received requests for mean change and outlier analyses of laboratory data from the Safety Review Team in HFD 120.
  - (a) In addition to those analyses, provide the following analyses of the vital signs and ECG data for the groupings used in the NDA ( — EPI, — DPN, and PHN):
    - Tabulations of outliers for each of the respective weight, vital sign, and ECG parameters.  
For outlier criteria that consider decreases/increases in values, your analyses should include only subjects with normal results (within normal range) prior to treatment and that met the low/high outlier criteria at any time during treatment. These analyses should exclude post treatment follow up results.
    - Calculation of maximum and minimum change from baseline for each of the parameters  
This analysis should use the last lab value prior to starting study treatment as the baseline and the lowest/highest recorded lab result on treatment for the minimum/maximum result for a given subject.
    - Shift tables showing the change from normal, "high" or "low" values. The shift tables should take the following format:

Parameter*	Treatment group		
	Maximum [N (%)]		
	Normal	High	Low
Baseline [N (%)]			
Normal			
High			
Low			

Baseline = last value prior to starting medication  
 Normal: normal laboratory range; High: values above the normal range; Low: values below the normal range  
 \* e.g. creatinine kinase, systolic blood pressure, QT interval

- (b) With respect to creatinine kinase, AST, and ALT, additional shift tables should take the following form:

Laboratory parameter	Treatment group*		
	Maximum [N (%)]		
	Normal	2 to ≤ 3 x ULN	> 3x ULN
Baseline [N (%)]			
Normal			
High			
Low			

- (c) With respect to the DPN population, there may be some laboratory, vital signs, or ECG values that may be outside of the normal range at baseline, but which would be typical for this population. Examples include serum creatinine, serum glucose, or systolic blood pressure. For such parameters, shift tables should identify the patients whose values were abnormal at baseline and became even more abnormal at endpoint. Increases of 50% in laboratory values can be considered as "worsening of abnormality."

2. Provide the CRFs and narratives for the following patients:  
 ISSPTID 087\_079009 (neoplasm)  
 ISSPTID 087\_079017 (neoplasm)  
 ISSPTID 034\_009008 (neoplasm)  
 ISSPTID 035\_028101 (neoplasm)  
 ISSPTID 029\_034001 (neoplasm)
3. Provide detailed information regarding the symptoms, diagnosis, treatment, and outcome regarding the AE (lung fibrosis) that the following patients experienced: 045\_066002 and 014\_013006. Details regarding duration of treatment with study drug, dose at AE onset, and use of other medications should be included, if available.
4. Submit an integrated safety data set for patients in DPN controlled trials that takes the following format:

ISSPTID	PROT	CPEVENT	PAINSC	DUR DM	DUR DPN	NEP RX	ACET	RXGRP	COMP	AGE	SEX

ISSPTID: ISS patient ID

PROT: protocol number

CPEVENT: visit type

1 = baseline

2 = termination (endpoint)

PAINSC: pain score at that visit

DURDM: duration of diabetes mellitus

DURDPN: duration of pain due to DPN (months)

NEPRX: prior neuropathic pain medications

1 = gabapentin only

2 = NSAIDs only

3 = opiates only

4 = benzodizepines only

5 = tricyclic antidepressants only

6 = gabapentin + TCA

7 = gabapentin + TCA + (NSAID, or opiate, or benzodiazepine, or other)

8 = none

9 = other

ACET: patient used acetaminophen during that week for pain relief

1 = yes

2 = no

RXGRP: Assigned double-blind treatment group

COMP: Patient completed the trial (i.e. did not withdraw from the study)

1 = yes

2 = no

AGE: patient's age at randomization/enrollment

SEX: patient's sex

5. In your review of renal function in DPN subjects, you state that "compared to 1.1% of placebo patients, no pregabalin patients had a doubling of their creatinine." We would like to review the data that support this statement. Provide a dataset that

includes all placebo and pregabalin patients from DPN controlled studies who had increases in creatinine. Also, provide a table showing the number and percent of subjects who had doubling of their creatinine.

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/s/

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Lisa Malandro  
3/24/04 10:35:56 AM

3/5/04

### NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-446  
Trade Name: Lyrica™ (pregabalin) Capsules  
Generic Name: N/A  
Strengths: 25, 50, 75, 100, 150, 200, 225, and 300 mg

Applicant: Pfizer Global Research & Development

Date of Application: October 30, 2003  
Date of Receipt: October 31, 2003  
Date clock started after UN: N/A  
Date of Filing Meeting: December 11, 2003 (HFD-170 only) and December 16, 2003 (joint filing meeting with HFD-120)  
Filing Date: December 30, 2003  
Action Goal Date (optional): User Fee Goal Date: April 30, 2004

Indication requested: Neuropathic pain associated with diabetic neuropathy

Type of Original NDA: (b)(1)  (b)(2) \_\_\_\_\_  
OR

Type of Supplement: (b)(1) \_\_\_\_\_ (b)(2) \_\_\_\_\_

NOTE: 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 is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S \_\_\_\_\_ P   
Resubmission after withdrawal?  No  Resubmission after refuse to file?  No   
Chemical Classification: (1,2,3 etc.)  1 \_\_\_\_\_  
Other (orphan, OTC, etc.) \_\_\_\_\_

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

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

User Fee ID # 4609

Clinical data? YES  NO, Referenced to NDA # \_\_\_\_\_

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES  NO

If yes, explain:

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)]?

N/A YES  NO

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?  N/A YES NO

• Does the submission contain an accurate comprehensive index?  YES NO

• 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:

• If an electronic NDA, does it follow the Guidance? N/A  YES NO  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format?  
 All

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A  YES NO

• Is it an electronic CTD? N/A  YES  NO  
**If an electronic CTD, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format?  
~~All~~

Additional comments:

• Patent information submitted on form FDA 3542a?  YES NO

• Exclusivity requested? YES, 5 years NO  
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature?  YES 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 . . ."

- Financial Disclosure forms included with authorized signature?  YES NO  
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)?  YES NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS?  YES NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.  
 YES
- List referenced IND numbers: IND 53,763
- End-of-Phase 2 Meeting? Date June 17, 1999  
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meetings? Dates June 7, 2000; July 17, 2002  
 If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS?  YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?  N/A YES NO
- Has DOTCDP been notified of the OTC switch application?  N/A YES NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment?  
If no, did applicant submit a complete environmental assessment?  
If EA submitted, consulted to Nancy Sager (HFD-357)?      YES       NO  
    YES      NO  
    YES      NO
- Establishment Evaluation Request (EER) submitted to DMPQ?       YES      NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)?       N/A      YES      NO

Also see NDA Regulatory Filing Review for NDA 21-723, 21-724       J

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ATTACHMENT

MEMO OF FILING MEETING

DATE: December 11, 2003

BACKGROUND: NDA 21-446 was submitted for four indications. Each indication has been administratively split into its own NDA. NDA 21-446 is a priority review for neuropathic pain associated with diabetic neuropathy. IND 53,763 was placed on partial clinical hold on February 27, 2001. At the time of the filing meeting, the partial clinical hold was still in effect.

ATTENDEES: Celia Winchell, MD; Suresh Doddapaneni, PhD; Jerry Cott, PhD; Mwango Kashoki, MD, MPH; Eric Duffy, PhD; Sue-Chih Lee, PhD; Dan Mellon, PhD; Carolanne Currier; Katherine Bonson, PhD; Sharon Hertz, MD; Ravi Harapanhalli, PhD; Lisa Malandro.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer*</u>
Medical:	Mwango Kashoki, MD, MPH
Secondary Medical:	N/A
Statistical:	Ling Chen, PhD
Pharmacology:	Jerry Cott, PhD
Statistical Pharmacology:	
Chemistry:	Sharon Kelly, PhD
Environmental Assessment:	Florian Zielinski
Biopharmaceutical:	Sue-Chih Lee, PhD
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Carolanne Currier
Regulatory Project Management:	Lisa Malandro
Other Consults:	CSS (Kit Bonson, PhD) HFD-550 (Wiley Chambers, MD)

\*The reviewers listed are the assigned reviewers from HFD-170. This NDA is being reviewed in concurrence with HFD-120. Please see filing reviews for NDA 21-723, 21-724 for additional assignments.

Per reviewers, are all parts in English or English translation?  YES  NO  
 If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site inspection needed:  YES  NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_  NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

		<input type="checkbox"/> N/A	<input type="checkbox"/> YES	<input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	NA <input checked="" type="checkbox"/>	FILE _____	REFUSE TO FILE _____	
STATISTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____	
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____	
	• Biopharm. inspection needed:		<input type="checkbox"/> YES	<input type="checkbox"/> NO
PHARMACOLOGY	NA _____	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____	
	• GLP inspection needed:		<input type="checkbox"/> YES	<input checked="" type="checkbox"/> NO
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE _____	
	• Establishment(s) ready for inspection?		<input checked="" type="checkbox"/> YES	<input type="checkbox"/> NO
	• Microbiology		<input type="checkbox"/> YES	<input checked="" type="checkbox"/> NO

ELECTRONIC SUBMISSION: Yes, in CTD format.

Any comments:

This application contains four indications. Each indication has been administratively split into an individual NDA (NDA 21-723, 21-724

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

- \_\_\_\_\_ The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- \_\_\_\_\_ No filing issues have been identified.
- Review issues to be communicated by Day 74. See letter.

**ACTION ITEMS:**

- Document filing issues conveyed to applicant by Day 74.

\_\_\_\_\_  
 Lisa Malandro  
 Regulatory Project Manager, HFD-170

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/s/

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Lisa Malandro  
3/5/04 11:10:30 AM  
CSO

**Malandro, Lisa**

**From:** Malandro, Lisa  
**Sent:** Friday, February 27, 2004 11:01 AM  
**To:** 'Bammert, James'  
**Cc:** Parker, Jonathon M (Regulatory Affairs); Malandro,  
**Subject:** NDA 21-446 Pregabalin Biopharmaceutics Request

*Biopharm IR*  
*Feb. 27, 2004*

Jim,

The Biopharmaceutics reviewer has requested the following information. Please submit it as an amendment to the application at your earliest convenience.

1. Provide a list of formulation numbers for the formulations used in each Phase 3 clinical trial. It appears that there are two sets of designations for each formulation, one with numbers only and the other with a combination of numbers and letters. Please include both designations in the list.
2. The formulation numbers for the market-image capsules (#53, 62-68) are different from those for the clinical trial formulations. Indicate the differences (e.g., capsule size, etc.) between the market-image formulations and the corresponding clinical trial formulations. In addition, demonstrate that market-image formulations are bioequivalent to the clinical trial formulations based on dissolution data in three dissolution media or justify why there is no need to do so.

Thanks

Lisa

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/s

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Lisa Malandro  
2/27/04 11:01:27 AM  
CSO

Malandro, Lisa

Clinical IR

Feb. 17, 2004

From: Malandro, Lisa  
Sent: Tuesday, February 17, 2004 5:31 PM  
To: 'Bammert, James'  
Cc: 'Parker, Jonathon M (Regulatory Affairs)'; Malandro, Lisa  
Subject: NDA 21-446 Pregabalin Clinical Request

Contacts: James Bammert

Jim,

As follow-up to today's teleconference, the Medical Officer has the following requests:

- Submit within the SCS, a new dataset entitled NEWDOSE which can be used to identify patients with any pregabalin exposure. This data set should include all of the variables (columns) that currently exist in the NEWDOSE1 and NEWDOSE2 datasets, and should include data for all 8666 patients with pregabalin exposure. As discussed in this afternoon's teleconference, the variable 'TREAT1' will represent double-blind treatment assignment and coding for this variable will be consistent across all other datasets.
- Provide explanations/instructions regarding how the following tables in the Summary of Clinical Safety (clinsafety.pdf) were obtained using the datasets that are provided in the NDA:
  - Table 4, Summary of exposure to pregabalin, controlled studies, all indications
  - Table 5, Summary of exposure to pregabalin, combined controlled and uncontrolled studies, all indications
  - Table 6, Summary of cumulative exposure to pregabalin by dosage range, combined controlled and uncontrolled studies - all indications
  - Table 7, Summary of Adverse Events in >2% of all pregabalin-treated patients by decreasing frequency, all controlled studies
- To facilitate review of AEs in the DPN and PHN populations without the need for repeated subsetting and removal of unused rows from studies not included in the relevant study pool, provide dataset files containing adverse event (AE) data from placebo-controlled trials for each the following conditions (1) pain due to diabetic neuropathy, (2) postherpetic neuralgia, and (3) neuropathic pain

Trials to be included in (1) are: 014, 029, 040, 131, 149, and 173.

Trials to be included in (2) are: 030, 045, 127, 132, and 196

Trials to be included in (3) are all trials in (1) and (2) above

Each of the datasets should contain the following variables (columns):

- All of the variables in the current pooled AE dataset ("AE.xpt")
- "STUDYMED", defined as the type of study medication received, where 1 =

pregabalin and 2 = placebo

Please submit a response as an electronic amendment to the NDA. If I can be of assistance, please do not hesitate to contact me.

Thanks,

Lisa

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Lisa Malandro  
2/23/04 03:45:15 PM  
CSO

**Malandro, Lisa**

*Clinical IR*

*Feb. 13, 2004*

**From:** Malandro, Lisa  
**Sent:** Friday, February 13, 2004 2:28 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Pregabalin Clinical Information Request

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Jonathan,

The medical officers have requested that we arrange a teleconference so that they can discuss some issues they are encountering with how the data are presented. Specifically, it would be helpful if Pfizer had one person physically sitting in front of a computer with the datasets open so that the reviewers can walk them through a demonstration of the difficulties they are having.

Some specific concerns that the Medical Officer has asked be addressed are described below:

- In the AE.xpt data set, there is no RXGRP variable by which patient exposure can be determined. There is a TREAT1 variable, however, there several subjects who do not have a treatment code. Are all of these subjects "de novo" subjects (i.e. subjects who directly entered into open-label studies)? Additionally, there is no explanation/description of the TREAT1 variable in the data definition table. The variable appears to correspond to treatment assignment in the controlled studies only. This, however, makes it difficult to ascertain treatment (dose) assignment for subjects in the open-label studies.
- The reviewer has joined several data sets for ease of data analysis (e.g. demo.xpt and AE.xpt). When attempts have been made to analyze the data by treatment assignment, this has not been possible since TREAT1 in the ae.xpt dataset is coded differently than TREAT in the demo.xpt dataset. For example, under TREAT1, subjects who received 50 mg/day pregabalin are coded as 50 mg/day PGB BID or 50 mg/day PGB TID. On the other hand, under TREAT, subjects are coded as 50 or 50 BID. Are these subjects the same or not? Neither the definition table or the derived dataset requirements document provides the appropriate explanation.
- Similarly, in some data tables, there are no data entered for certain variables. For example, in the data set dich.xpt, there are no data entered under the variable TREAT1. It is important to know whether this variable is the same as TREAT1 in the ae.xpt data set, especially because I would like to join these datasets.
- Contrary to the Instructions to the Reviewer, there is no single NEWDOSE dataset from which exposure is supposed to be ascertained. Instead, there are two separate datasets: NEWDOSE1 and NEWDOSE2. There is no explanation/description of these data sets in the data definition table or in the derived dataset requirements document. It appears that these datasets are simply divisions of all of the patient data into halves, but this has not been

specifically stated. When the datasets are analyzed separately to identify patients with any pregabalin exposure (as per the Instructions to the Reviewer), it is found that there are 4118 patients in NEWDOSE1 and 5093 in NEWDOSE 2, the total of which is clearly greater than the 8666 unique patient exposures that the Sponsor claims. Although joining of these two data sets using JMP and subsequent analysis for exposure data can yield 8666 patients who have been exposed, duplication of the variables/columns in the combined dataset (eg. TREAT for NEWDOSE1 and TREAT for NEWDOSE2) does not facilitate further analysis of the data (e.g. grouping by treatment assignment).

*Ultimately, what is necessary for full and facile data analysis is the following:*

- A data definition table in which the variable names (and their corresponding codes) are completely described. For example, "In the NEWDOSE2 dataset, the TREAT variable/column has 16 subgroups (codes): 75, 150, 150 BID etc." TREAT should be defined (e.g. "patient's assigned study group in double-blind trial") as well as each of the codes for that variable (e.g. "75 = treatment with 75 mg/day in double blind trials"). If the same variable/column is used in multiple datasets, then the definition of that variable/column and its subgroups must be consistent across datasets.

Thanks,  
LisaM

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/s/

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Lisa Malandro  
2/23/04 03:40:55 PM  
CSO

**Malandro, Lisa**

*Pharm Tox IR*

*Feb. 4, 2004*

**From:** Malandro, Lisa  
**Sent:** Wednesday, February 04, 2004 3:52 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Request for Correction

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Jonathan,  
I received the following comment/request from the Pharmacology/Toxicology Reviewer.

The photos of the lesions are mislabeled. For example the image named Figure F-6.jpg is named FIGURE F-2 on the bottom of the frame.

Please correct the labels on the actual image to avoid mix-ups.

Lisa

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/s/  
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Jackie Ware  
1/28/04 01:36:32 PM  
CSO  
IR sent 1/24/04 via email

DMETS Review  
2/19/04

Ware, Jacqueline H

---

From: Mahmud, Alina  
Sent: Tuesday, February 03, 2004 2:07 PM  
To: Ware, Jacqueline H; Beam, Sammie; Culley, Kimberly  
Cc: Malandro, Lisa  
Subject: RE: DFS Email - N 000 08-Dec-1995 - Review

I agree with your concerns and think that a memo should be filed. That would be great if you could DFS this email as a memo.

Thanks,  
Alina

LCDR Alina R. Mahmud  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Rm 6-34  
Tele: (301) 827-0916  
FAX: (301) 443-9664

-----Original Message-----

From: Ware, Jacqueline H  
Sent: Tuesday, February 03, 2004 2:00 PM  
To: Mahmud, Alina; Beam, Sammie; Culley, Kimberly  
Cc: Malandro, Lisa  
Subject: RE: DFS Email - I N 000 08-Dec-1995 - Review

Thanks, Alina. But I have a question for you...  
Is it possible for DMETS to put a short memo in the current NDA file referencing the IND consult & indicating that the name doesn't have to be resent until 90 days prior to approval? Alternatively, I could DFS this email as a memo re: NDA tradename?

I'm concerned that anyone reading the NDA file at some future time won't be able to easily understand the sequence of events. Specifically, with some memo in the NDA file, it will look like no name review was ever done for the NDA until 90 days prior to approval.

Just let me know what you think.

Thanks, Jackie

-----Original Message-----

From: Mahmud, Alina  
Sent: Tuesday, February 03, 2004 12:15 PM  
To: Ware, Jacqueline H; Beam, Sammie; Culley, Kimberly  
Cc: Malandro, Lisa  
Subject: RE: DFS Email - I N 000 08-Dec-1995 - Review

Good, glad to hear that. Please submit the name for re-review 90 days prior to approval.

Thanks,  
Alina



**Malandro, Lisa**

*Clinical IR*  
*Jan. 23, 2004*

**From:** Malandro, Lisa  
**Sent:** Friday, January 23, 2004 11:27 AM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Subject:** NDA 21-446 Clinical Information Request

**Importance:** High

**Contacts:** Jonathon M Parker (Regulatory Affairs)

Hi Jonathan,

I received the following request regarding studies 014, 029, and 131 from our Medical Officer:

1. Provide the location (volume and page number) in the NDA for the tabulation of efficacy by study site using the baseline observation carried forward (BOCF) analysis of the difference in the mean pain score
  - at endpoint
  - during the final week of treatment
2. If the above information is not available in the NDA, provide it.
3. Clarify why; in the available data regarding treatment-by-center interactions, the center numbers in the tables and graphs do not match the actual site numbers. For example, in Appendix D2 of the report for protocol 014, the table on page 551 (entitled "Difference in Mean Pain Score between Placebo and PGB 600 at Endpoint, Center-by-Treatment Interaction) shows data for various numbered study centers. However, these numbers do not match the actual site numbers provided in Table 1 of that same report.

Thanks,  
Lisa

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Lisa Malandro  
1/23/04 11:25:46 AM  
CSO

**Malandro, Lisa**

*Biopharm IR*  
*Jan. 21, 2004*

**From:** Malandro, Lisa  
**Sent:** Wednesday, January 21, 2004 2:16 PM  
**To:** 'Parker, Jonathon M (Regulatory Affairs)'  
**Cc:** Ware, Jacqueline H  
**Subject:** NDA 21-446 Clinical Pharmacology/Biopharmaceutics Information Request  
**Contacts:** Jonathon M Parker (Regulatory Affairs)

Jonathan,  
Following are preliminary requests from the Biopharmaceutics reviewer. Response to them is requested.  
If you have any questions, please do not hesitate to contact me.  
Thanks,  
Lisa

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS  
INFORMATION REQUEST**

**A. Population PK analysis: RR 764-03296**

1. Explain how 95% confidence intervals of parameter estimates were constructed. Was bootstrapping of parameters conducted?
2. For evaluation of drug interaction with diuretics and antidiabetic medications, the ratio and 90% CI of mean clearance values was provided. Explain how the ratio and 90% CI were computed. Were posthoc individual clearance estimates used for this purpose?
3. Concomitant diuretics were pooled as one category of drugs in the analysis. The same was done with antidiabetics. To facilitate our evaluation of the analysis, provide the following information:
  - a. In the dataset, 163 patients took diuretics concomitantly. Indicate the diuretics used by these patients and their dose and dosing regimen. For each specific diuretic medication, indicate how many patients were on it.
  - b. Provide similar information for oral antidiabetics.
  - c. Provide a .xpt file that includes all subjects and contains information on subject ID, individual pregabalin clearance estimate ( $CL_i$ ), creatinine clearance, specific diuretic and antidiabetic drug names. An example is given below:

ID	$CL_i$	CL <sub>cr</sub>	Oral Antidiabetic	Diuretics
1	46	80	X <sub>1</sub>	.
2	41	100	.	.
3	33	60	.	Y <sub>1</sub>

- d. For each diuretic drug, provide a scatter plot of  $CL_i$  vs. CL<sub>cr</sub> for patients taking the specified diuretic and patients not taking any diuretics on the same graph. Use different symbols for easy visualization. The sponsor may present all data points in one scatter plot if the presentation is clear.
- e. Provide similar scatter plots for patients taking antidiabetic medications.

**B. *Exposure-Response for pain: Study 75400011***

It is unclear how the simulations were performed to yield results as shown in Fig. 5 on Page 36 of RR754-00011. It appears that data for Study 149 were fitted using the final exposure-response model and the parameter values obtained were employed along with the covariates for Study 149 to simulate 1000 index datasets. The simulated mean pain scores were then compared to those observed from the other 8 studies. Clarify and provide the simulation codes and parameter values used in the simulation.

**C. *Exposure-Response for adverse events: Study 75400012***

1. Provide summary tables by study showing the incidence rate (n/N & %) and severity of adverse events (somnolence and dizziness only; n/N & %) for each pregabalin treatment arm at various times during the study.
2. Provide rationale for setting constant incidence rate over the treatment period in the model.
3. Provide rationale for pooling data from all studies including seizure patients with concomitant medications that may contribute to the adverse events of interest.

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/s/

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Lisa Malandro  
1/21/04 03:50:27 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

74 DAY LETTER  
Jan, 9, 2004

FILING COMMUNICATION

NDA 21-446  
NDA 21-723

Pfizer Global Research and Development  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS  
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to your October 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 20/50/75/100/150/200/225/300 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 30, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

**Clinical**

The proposed [ ] has not been replicated in clinical trials and, therefore, may not be supported by the submitted data.

**Pharmacology/Toxicology**

1. The significant dermatopathology in the rat and monkey is of concern, especially for diabetic patients who are prone to infection and problems with wound healing. The risk-to-benefit ratio of pregabalin in this patient population will be evaluated independently in light of the increased susceptibility to delayed wound healing.
2. The finding of hemangiosarcoma in the mouse carcinogenicity studies is of concern. Both Divisions will continue to evaluate the risk-to-benefit ratio for each indication during the review process.

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

**Clinical**

Provide a rationale for a full waiver from the requirement for studies of efficacy, safety, and PK data in patients 17 years of age or younger who have pain due to peripheral diabetic neuropathy. The rationale should be based on the epidemiology of the disease in these pediatric patients.

**Abuse Liability**

1. Provide full binding data represented as  $K_d$ ,  $K_i$  or  $pK_d$  values.
2. Provide data from human abuse potential studies with gabapentin, if available, for comparison with data from similar studies using pregabalin. Include all available subjective ratings from individual Addiction Research Center Inventory (ARCI) and Visual Analog Scale (VAS) instruments.
3. Provide all information on reports of "euphoria" and other central nervous system adverse events from clinical studies with gabapentin, if available, or comparison with similar clinical studies with pregabalin.

**Pharmacology/Toxicology**

1. Submit legible photograph-quality images of the tail lesions in both species.
2. Submit any additional information you may have or are able to obtain regarding the etiology/pathology of these lesions.
3. File sp1994.pdf is not fully functional in Adobe Acrobat. Submit a replacement of the file to the EDR.

Please respond only to the above requests for additional information. 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, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

  
{See attached electronic signature page}

Bob Rappaport, M.D.  
Director  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

-----  
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/s/

-----  
Bob Rappaport  
1/9/04 05:23:12 PM

**Malandro, Lisa**

*Sponsor Response to  
Clinical IR  
Dec. 19, 2003*

**From:** Parker, Jonathon M (Regulatory Affairs)  
[Jon.Parker@pfizer.com]  
**Sent:** Friday, December 19, 2003 5:03 PM  
**To:** 'Malandro, Lisa'; Parker, Jonathon M (Regulatory Affairs)  
**Cc:** Ware, Jacqueline H  
**Subject:** RE: NDA 21-446, request for information  
**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Lisa,

As per our discussion this afternoon, I'm providing for you the location of the rescue medication information. The location of the this information is listed by section or appendix and page number within the research report. Additionally, a "see also" section provides more detail on the prohibited meds.

Study

- 14 Appendix D.21, page 1923 of 2097, see also Table 9, page 34 of 2097
- 29 Appendix D.21, page 1729 of 1963, see also Table 11, page 40 of 1963
- 40 Section 4.5.2, page 72 of 1549, see also Section 9.3.2, page 284 of 1549
- 131 Appendix D.3, page 474 of 1940, see also Appendix A.8, page 238 of 1940
- 149 Section 5.1.2.2.2, page 88 of 3835, see also Section 9.3.2, page 400 of 3835

For Questions 1 & 2, as agreed, we will provide our the definition information to you next week (by 12/24/03). I will send it to you and Dr. Jani via e-mail. Additionally, we will include our timing for rescue medication data set (Question #2). At this point, the week of December 29th or January 5th seem possible.

As a point of clarification, for Question 2, is the statistician interested in rescue medication (i.e. acetaminophen/paracetamol), as stated, or prohibited meds? I just want to be sure we provide the right information. Also, given that the "diardiar" data set is a very large data set, would it be beneficial for the statistician to receive a new data set with just those patients information?

If you could let me know.

Thanks and have a great holiday break

**Jonathon M. Parker**

Worldwide Regulatory Strategy  
Pfizer Global Research & Development  
(734) 622-5377  
Fax (860) 715-8727  
Cell (734) 646-7657  
Jon.Parker@pfizer.com

-----Original Message-----

**From:** Malandro, Lisa [mailto:MalandroL@cder.fda.gov]  
**Sent:** Friday, December 19, 2003 12:01 PM  
**To:** Parker, Jonathon M (Regulatory Affairs)  
**Cc:** Ware, Jacqueline H  
**Subject:** NDA 21-446, request for information

HI Jonathan,

Our statistician is having difficulty finding the detailed information about the rescue medication for the DPN studies. Is it possible for you to let us know what the exact location is?

Also, she requests that you provide the following information as soon as possible:

1. The definitions for the proportion of patients who took acetaminophen and the proportion of patients who took prohibited pain medications. (Basically, I need to know how the proportions were calculated.)
2. Put an indicator variable for rescue medication in the diardiar data set for studies 131,149, 014, 029, 040.

I'm here for the rest of the day today, but will be out of the office next week. Happy holidays,  
Lisa

"MMS <secure.pfizer.com>" made the following annotations on 12/19/2003 12:00:44 PM

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This message was sent in secure form from cder.fda.gov CDER Stamp  
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"MMS <secure.pfizer.com>" made the following annotations on 12/19/2003 05:03:16 PM

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1/23/2004

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/s/

-----  
Lisa Malandro  
1/23/04 12:49:34 PM  
CSO

NDA Acknowledgement  
Nov. 25, 2003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-446  
21-723

Pfizer Global Research and Development  
800 Plymouth Road  
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS  
Associate Director

Dear Mr. Parker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: LYRICA™ (pregabalin) Capsules, 20/50/75/100/150/200/225/300 mg

This application has been administratively split by the Agency according to indication. Two applications have been submitted to HFD-170, details follow:

Our Reference Number:		NDA 21-446	NDA 21-723
Indication:		Neuropathic pain associated with diabetic peripheral neuropathy	Neuropathic pain associated with herpes zoster (postherpetic neuralgia)
Review Priority Classification:		Priority (P)	Standard (S)
Date of Application:		October 30, 2003	October 30, 2003
Date of Receipt:		October 31, 20003	October 31, 20003

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on December 30, 2003 in accordance with 21 CFR 314.101(a). If we file the application for diabetic peripheral neuropathy (NDA 21-446), the user fee goal date will be April 30, 2004. If the postherpetic neuralgia application (NDA 21-723) is filed, the user fee goal date will be August 31, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review of NDA 21-446, but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

NDA 21-446  
NDA 21-723  
Page 2

Please cite the NDA numbers listed above at the top of the first page of any communications concerning these applications. Address all communications concerning these NDAs as follows:

Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction Drug Products  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

 *(See appended electronic signature page)*

Lisa Malandro  
Regulatory Project Manager  
Division of Anesthetic, Critical Care  
and Addiction Drug Products, HFD-170  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

-----  
Lisa Malandro  
11/25/03 11:51:55 AM

9/25/03

## NDA ACTION PACKAGE CHECKLIST

NDA 21-446	Efficacy Supplement Type SE-	Supplement Number N/A
Drug: LYRICA (Pregabalin) Capsules		Applicant: Pfizer, Inc.
RPM: Lisa Malandro		HFD-170 <span style="float: right;">Phone # 301-827-7410</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1/2040100
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		April 30, 2004 (original) July 31, 2004 (after clock extension)
❖ 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
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" 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.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
	L. Ripper July 29, 2004 L. Malandro March 5, 2004
❖ Actions	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	June 4, 2004
• Most recent applicant-proposed labeling	July 2, 2004
• Original applicant-proposed labeling	March 17, 2004 October 30, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings (indicate dates of reviews and meetings)	DSRCs June 3, 2004 DMETS December 10, 2003 & May 18, 2004 DDMAC-via labeling meeting attendance
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	July 9, 2004 October 30, 2004
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	July 29, 2004 documented in AE letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
	Yes
❖ Memoranda and Telecons	
	Yes

❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	June 17, 1999
• Pre-NDA meeting (indicate date)	July 23, 2003, July 17, 2002 (minutes not generated)
• Pre-Approval Safety Conference (indicate date; approvals only)	May 18, 2001 March 22, 2004
• Other	Regulatory Briefing Minutes May 26, 2004 Controlled Substances Meeting May 17, 2004
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Dr. Meyer July 28, 2004 Dr. Rappaport June 28, 2004 Dr. Winchell June 3, 2004
❖ Clinical review(s) (indicate date for each review)	Dr. Kashoki May 20, 2004 DRUDP May 6, 2004 Dr. Chambers April 2, 2004
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	June 4, 2004
❖ Statistical review(s) (indicate date for each review)	Dr. Chen April 29, 2004 Dr. Permutt April 29, 2004 Dr. R. Kelly May 10, 2004 Dr. Lin May 6, 2004
❖ Biopharmaceutical review(s) (indicate date for each review)	Dr. S. Lee March 22, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	March 31, 2004
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	June 7, 2004
• Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	Dr. E. Duffy July 29, 2004 Dr. R. Harapanhalli June 4, 2004 Dr. S. Kelly May 24, 2004
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	February 24, 2004
• Review & Environmental Impact Statement (indicate date of each review)	February 24, 2004
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A

❖ Facilities inspection (provide EER report)	Date completed: June 22, 2004 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	Dr. Hastings June 24, 2004 Dr. Mellon June 3, 2004 Dr. Cott May 28, 2004 Dr. Fisher May 20, 2004 Dr. Peters February 9, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	N/A
❖ CAC/ECAC report	December 21, 2000

Appears This Way  
On Original

32 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

PPG Regulatory Library  
Pfizer Inc  
150 East 42nd Street 3-46  
New York, NY 10017  
Tel 212 733 3946 Fax 212 857 3516  
Email felicia.feldman@pfizer.com

---



Felicia A. Feldman  
Director

October 16, 2003

Food and Drug Administration  
Mellon Client Services Center  
Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

Re: Prescription Drug User Fees

Dear Sir or Madam:

As required by the Prescription Drug User Fee Act of 2003, enclosed is the NCE application fee in the amount of \$573,500 for Pfizer's New Drug Application for Lyrica (pregabalin). The NDA number for this submission is 21-446 and has been assigned User Fee ID Number 4609. This submission will be filed to the Food and Drug Administration on or about October 31, 2003.

If you require further assistance, please contact me at 212-733-3946.

Sincerely,

A handwritten signature in cursive script, appearing to read "Felicia A. Feldman".

Felicia A. Feldman

cc: L. Castro  
E. Harrigan  
R. Wittich  
R. Clark  
M. Phillips (AA)  
P. Conwell

# PRESCRIPTION DRUG USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

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

Pfizer Global Research and Development  
Attn: Jonathon M. Parker, RPh, MS  
Ann Arbor Laboratories  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  
21-446

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
 YES  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:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

TELEPHONE NUMBER (Include Area Code)

734 ) 662-5377

PRODUCT NAME

Lyrica (pregabalin) Capsules

6 USER FEE I.D. NUMBER  
4609

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

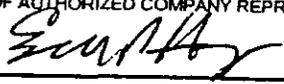
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Department of Health and Human Services  
Food and Drug Administration  
CFR, HFM-99  
1 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and  
12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

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NATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE  
Senior Vice President, Worldwide Regulatory  
Affairs and Quality Assurance

DATE  
10/15/2003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 53,763

*Type A meeting mins.  
July 23, 2003*

Parke-Davis Pharmaceutical Research,  
Division of Pfizer, Inc.  
2800 Plymouth Road  
Ann Arbor, MI 48105

Attention: Johathon M. Parker, R.Ph., M.S.  
Associate Director, Regulatory Strategy, Policy and Registration  
Worldwide Regulatory Affairs

Dear Mr. Parker:

Please refer to the meeting between representatives of your firm and FDA on June 26, 2003. The purpose of the meeting was to seek the Division's agreement that Pfizer has adequately addressed the issue that efficacy for pregabalin is not attributable to nerve damage in diabetic peripheral neuropathy (DPN) patients and to discuss the need, if any, for an additional clinical study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7407.

Sincerely,

*{See appended electronic signature page}*

Lisa Marie Malandro  
Regulatory Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## MINUTES OF TELECON

DATE: February 8, 2001

APPLICATION NUMBER: IND 53,763

BETWEEN:

Name: Tim Anderson, D.V.M.	Drug Safety Evaluation
Steve Duddy, Ph.D.	Drug Safety Evaluation
Doug Feltner, M.D.	Clinical Development
Alexandra Fernandes, M.D.	Regulatory Affairs
Elizabeth Garofalo, M.D.	Clinical Development
Stephen Gracon, D.V.M.	Regulatory Affairs
Jim Herman, Ph.D.	Drug Safety Evaluation
Toni Hoover, Ph.D.	Global Project Management
Richard Kavoussi, M.D.	Clinical Development
Ken King, Ph.D.	Regulatory Affairs
William Kluwe, Ph.D.	Drug Safety Evaluation
Alan Kugler, Ph.D.	Clinical Development
Dave Pegg, Ph.D.	Drug Safety Evaluation
Robin Pitts, R.Ph	Regulatory Affairs
Robert Michael Poole, M.D.	Clinical Development
Byron Scott, R.Ph	Regulatory Affairs
Uma Sharma, Ph.D.	Clinical Development
Kirk Taylor, M.D.	Clinical Development
Zbigniew Wojcinski, D.V.M.	Drug Safety Evaluation

Representing: ParkeDavis/Pfizer

AND

Name: John Jenkins, M.D., Director, ODE II  
Cynthia G. McCormick, M.D., Director  
Tom Papoian, Ph.D., Supervisory Pharmacologist  
Belinda Hayes, Ph.D., Pharm/Tox Reviewer  
Sharon Hertz, M.D., Medical Reviewer  
Laura Governale, Pharm.D., Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

SUBJECT: Partial Clinical Hold for pregabalin

The sponsor was informed that IND 53,763 for the treatment of neuropathic pain will be placed on partial hold due to the findings presented in the Exec.CAC hearings on December 12, 2000. Until additional information is known regarding the tumorigenic mechanism of hemangiosarcoma in mice, and the relevance of this finding to humans, the potential risk is considered unacceptable to the neuropathic pain patient population.

Graded criteria have been established by the Agency to determine which patients may be considered for ongoing treatment with pregabalin. Only patients considered refractory to traditional treatments will be permitted to participate in further clinical trials. For trials with duration of less than 12 weeks, patients must have failed treatment with a tricyclic antidepressant (TCA) and gabapentin. For trials with a duration of greater than 12 weeks, patients must have failed treatment with a tricyclic antidepressant (TCA), gabapentin, and a third line agent (opioid, another anticonvulsant, local anesthetic, etc.) in order to qualify for enrollment. The language of the informed consent and the investigator's brochure will be amended in conjunction with the Division of Neuropharmacological Drug Products to reflect the current information. The sponsor was advised to submit a proposal on how to inform patients who have already been exposed to pregabalin. [

]

The clinical trials intended to support of the NDA submission planned for August 2001, have already been completed. Since the currently running trials are not pivotal and not necessary to support the NDA, a partial hold on this IND will not affect the timeline for the NDA submission. The sponsor expressed concern whether this Division would refuse to file the NDA since the pivotal clinical trials were only 8-weeks in duration. The Division of Anti-Inflammatory and Ophthalmic Drug Products, which was previously responsible for the review of this indication, had agreed to an 8-week trial design for their pivotal studies even though the standard duration for a chronically administered drug is 12 weeks. The Division of Anesthetics, Critical Care and Addiction Drug Products agreed to respect this prior agreement. Should the partial hold be lifted due to resolution of the concern over the carcinogenicity of pregabalin, and pregabalin approved for the treatment of neuropathic pain, the Agency would welcome long term data on the BID regimen as a Phase 4 commitment.

[ ] the sponsor indicated that they would stop the ongoing clinical investigations since none of the currently enrolled patients fit the new entry criteria as defined in this telecon. All centers will be notified by Monday, February 12, 2001. The trial for [ ] criteria. The trial for [ ]

]

The telecon adjourned.



---

Laura Governale, Pharm.D.  
Regulatory Project Manager

/s/

-----  
Laura Governale

2/27/01 05:23:13 PM

Food and Drug Administration  
Rockville, MD 20857IND —  
IND 53,763

Warner-Lambert Company  
c/o Ann Arbor Laboratories  
Pfizer, Inc.  
Attention: Robin Pitts, R.Ph.  
Senior Manager, Worldwide Regulatory Affairs  
2800 Plymouth Road  
Ann Arbor, MI 48105

Response to Pfizer's ?'s  
Sept. 12, 2001

Dear Ms. Pitts:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pregabalin.

We also refer to your amendments dated August 31, 2000 (serial #213 and #193, respectively), containing a revised proposal for the pregabalin electronic submission (ERS) plan, and to your June 25, 2001, and July 30, 2001, emails, containing additional questions/clarifications regarding the pregabalin ERS.

We have completed our review of your submission and have determined that the overall plan is acceptable. In addition, we have provided responses to your questions listed in the submission and in your June 25, 2001, email. For ease of review, your questions are listed in bold print.

- 1. We would like to confirm with the Agency the following proposal for the Review Copies of the NDA application and we would also like to discuss with the Agency what additional portions of the paper review copy that can be eliminated. Our proposal is as follows:**

**For the submission of the NDA, we will submit a review copy of the technical sections (i.e., chemistry, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, clinical, and statistical) of the application in addition to the copy for archive (21CFR 314.50(1)).**

The paper review copy will have the following characteristics:

- Review copies will be a printout of the electronic archive copy.
- Hypertext links (with navigational value) in electronic archive will not be functional in the paper review copies. Most hypertext-linked text will contain a short description of the link's destination. For example, "see Appendix A.2" and "presented in Section 4.6.2". Hypertext links for the Item 4 CMC section will be detailed under a separate cover.

- Review copy volume numbers will appear in the Item Table of Contents.
- Review copy volume numbers may not appear in succession. This depends on the portions of the submission requested in the review copy.

You must document each and every cross-reference in some manner. Important references for review should be easy to locate. In particular, it is difficult if a reference does not have at least the volume number and the page number; if the reference is to "Appendix A.4," and one has to browse the index to locate Appendix A.4, it is inefficient.

2. We would also propose that the following portions of the review copy not be submitted in paper:

- CMC section: methods validation reports
- Nonclinical pharmacology and toxicology sections: individual animal line listings
- Clinical sections: study report Appendices 16.1.3. to 16.4 as defined by the ICH E3 Structure and Content of Clinical Study Reports (July 1996)
- Case Report Forms
- Case Report Form Tabulations
- Investigator CV's

This proposal is acceptable given our comments to Question 1 above. However, at the time of NDA submission, please submit three paper copies of the method validation package.

3. a. At our June 7, 2000 meeting, the Agency requested SAS programs to be our provided. We propose to submit the following:

- SAS programs that perform the preplanned statistical analyses as defined in the inferential analysis plans for the studies of submitted indications. The programs will be provided as ASCII files. Please note that due to computer platform differences, these programs are not expected to be executable without modification. They are intended to serve as a reference to reviewers in understanding how the analyses were conducted and as a guide in modeling SAS code to verify analyses.
- Study specific SAS datasets on which the above programs are run. These datasets contain variables that are derived from the raw (CRF) data, for example, timepoint variables, calculated variables and patient population indicator variables. The datasets will be provided in SAS transport format.

It is acceptable, from an efficacy standpoint, for SAS programs and data to be confined in the first instance to the "pivotal" trials, with the understanding that the question of what weight to give to what trials is a matter of review. Therefore, we may request SAS programs and data for other studies. In addition, we request that you provide a list of definitions of the SAS variables in the SAS datasets. We have looked at your examples of define.pdf files

(contained in your email dated July 30, 2001) and they appear to be consistent with the electronic submission guidance format; however, it appears that the codes for many variables have not yet been entered without which we cannot perform the review.

Lastly, we ask that the data comprising the Integrated Summary of Safety be available in SAS transport files. Specifically, we are referring to tabulations of adverse events including a table of verbatim terms, mapped terms, patients' unique identification numbers, study number, dates of events, and medication/dose at the time of the event. Include the safety information from all clinical studies, including adverse events, serious adverse events, deaths, and discontinuations due to adverse events from the clinical pharmacology studies.

**b. We would also propose to submit only the SAS programs for the pivotal studies and would like confirmation that this is acceptable.**

This proposal is acceptable for the efficacy, but not the safety data, as noted in our response to Question 3 a. In addition to programs for inferential analysis of derived data sets, documentation of how these data sets were derived from CRF data may be very helpful.

**4. For clinical studies, please specify the studies where patient profiles should be provided (e.g. all clinical studies or clinical studies in epilepsy, pain.  J**

Please provide patient profiles for clinical studies in epilepsy and pain.

**5. For clinical pharmacology studies, we propose that patient profiles not be provided. Is this acceptable?**

This is acceptable. You will still be required to provide specific case report forms should particular questions arise during the review process.

**6. Please provide clarification on FDA request outlined in the pre-NDA meeting minutes: "In the dataset listing prior and concurrent medications, there should be a flag denoting medications that were being taken prior to the initiation of the study drug." Should the flag denote medications being taken prior to the initiation of the study drug and continuing during treatment or just those medications taken before initiation of the study drug or both?**

We suggest that you develop coding that identifies medications being taken prior to the study and stopped prior to enrollment with one designation, medications being taken prior to the study and continued during the study are with a second designation, and medications initiated during the study are with a third designation.

7. For clinical pharmacology prior and concurrent medications dataset, we propose not to include this flag denoting medications being taken prior to initiation of study drug. This dataset will include the medication start date, study day of medication start date and medication start time. Is this acceptable?

This is not acceptable because the variables you propose to include do not include any stop dates. Therefore, we will have no way of knowing whether one of the drugs the patient was on prior to the study was stopped or continued during the study. If you include stop dates, you could exclude the "flag" variable for the clinical pharmacology studies.

8. Please provide clarification on FDA request outlined in the pre-NDA meeting minutes: "All datasets should list the dates of the first and last study drug dose for each patient." Please clarify for open-label studies, should first dose date reflect first day of open-label medication or first day of pregabalin or should both dates be included?

For open-label trials, please include start and stop dates of the previous controlled trial medication as well as start and stop dates of the open-label trial medication.

9. For clinical pharmacology datasets, we propose not to include the dates of the first and last study drug dose for each patient. We will provide the medication dosing dataset which indicates what medication was taken at a particular point in time. Is this acceptable?

This is acceptable.

10. Clarification of FDA request outlined in pre- NDA meeting minutes: "Any adverse event dataset should include the investigator's verbatim term for the AE, the preferred term for the AE, and the system organ class (SOC)." Body system terminology will be used instead of the SOC.

Body system terminology is fine provided it serves the same purpose as the SOC (to group preferred terms by body system).

Lastly, we have the following request related to section 2.7, Item 6 Human Pharmacokinetics and Bioavailability, of your pregabalin ERS proposal. For population pharmacokinetic data and pharmacokinetic/pharmacodynamic data from clinical trials, please include demographics and any other relevant covariates in the data sets.

IND —  
IND 53,763  
Page 5

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

*{See appended  electronic signature page}*

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

*{See appended  electronic signature page}*

Cynthia McCormick, M.D.  
Director  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

-----  
Cynthia McCormick  
9/5/01 04:01:08 PM

Russell Katz  
9/12/01 10:46:17 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

*Parke-Davis Hold letter  
Feb. 27, 2001*

IND 53,763

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

Parke-Davis Pharmaceutical Research  
Division of Warner-Lambert Company  
2800 Plymouth Road, P.O. Box 1047  
Ann Arbor, MI 48106-1047

Attention: Robin Pitts, R.Ph.  
Manager, FDA Liason  
Worldwide Regulatory Affairs

Dear Ms. Pitts:

Please refer to your Investigational New Drug Application (IND) submitted July, 24, 1997, received July 25, 1997, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pregabalin (CI-1008) capsules.

We also refer to your amendment dated June 16, 2000, (serial # 173), and to the February 8, 2001, telephone conversation between representatives of your firm and this Division in which you were notified that this IND for the treatment of neuropathic pain will be placed on partial hold due to the findings presented in the Executive Carcinogenicity Assessment Committee (E-CAC) hearings on December 12, 2000. Until additional information is known regarding the tumorigenic mechanism of hemangiosarcoma in mice, and the relevance of this finding to humans, the potential risk is considered unacceptable to the neuropathic pain patient population.

In order for patients to continue in these trials, the patients must fit the criteria for refractoriness and be made aware of the risks by signing a revised informed consent form.

<b>Duration of Trial</b>	<b>Entry Criteria</b>
Less than 12 weeks	Patients must have failed treatment with both a tricyclic antidepressant (TCA) and gabapentin.
Greater than 12 weeks	Patients must have failed treatment with a tricyclic antidepressant (TCA), gabapentin, and a third line agent (opioid, another anticonvulsant, local anesthetic, etc.).

IND 53,763

Page 2

In order to treat neuropathic pain patients who are not refractory to other therapies, you must provide sufficient information concerning the mechanism of the carcinogenic effect of pregabalin in mice to allay concerns of a carcinogenic potential in humans.

Until you have submitted the required information, and we notify you that you may initiate the trials, you may not legally conduct the identified clinical studies under this IND.

Please identify your response to the clinical hold issues as a "CLINICAL HOLD COMPLETE RESPONSE." To facilitate a response to your submission, submit this information in triplicate to the IND. In addition, send a copy of the cover letter to Laura Governale.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

If we have additional comments or information requests not related to this clinical hold, we will notify you in approximately 30 days. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

Correspondence to this IND can be sent to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170  
Attention: Division Document Room, 9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at 301-827-7410.

Sincerely,

 *{See appended electronic signature page}*

Cynthia McCormick, M.D.  
Director  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

/s/

-----  
Cynthia McCormick  
2/27/01 06:43:33 PM

EXEC. CAC Minis.

Dec. 29, 2000

Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville, MD 20857

ND —  
IND —  
IND 53,763

Parke-Davis Pharmaceutical Research  
Division of Warner-Lambert Company  
Attention: Robin Pitts, R.Ph.  
2800 Plymouth Road, P.O. Box 1047  
Ann Arbor, MI 48106-1047

Dear Ms. Pitts:

Reference is made to the Agency's December 12, 2000 meeting of the Executive Carcinogenicity Committee (E-CAC) where results of pregabalin carcinogenicity studies (submitted June 16, 2000) were discussed.

As you requested, the official minutes of that meeting are enclosed. Please note, however, that the recommendations made by the E-CAC on carcinogenicity study evaluations are advisory and should not be interpreted as a measure of the approvability of your application.

If you have any questions, call Jacqueline H. Ware, Pharm.D, Regulatory Project Manager, at (301) 594-5533.

Sincerely,

/S/

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

*IND 53,763  
Partial Hold Telecon.  
Feb. 27, 2001*

IND 53,763

Parke-Davis Pharmaceutical Research  
Division of Warner-Lambert Company  
2800 Plymouth Road, P.O. Box 1047  
Ann Arbor, MI 48106-1047

Attention: Robin Pitts, R.Ph.  
Manager, FDA Liason  
Worldwide Regulatory Affairs

Dear Ms. Pitts:

Please refer to the telephone conference between representatives of your firm and FDA on February 8, 2001. The purpose of the meeting was to relay partial hold information for IND 53,763, pregabalin.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7410.

Sincerely,

*/S/*

Laura Governale, Pharm.D.  
Regulatory Project Manager  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Pre-NDA meeting  
minutes

Public Health Service

May 18, 2001

Food and Drug Administration  
Rockville, MD 20857

IND —  
IND 53,763

Parke-Davis Pharmaceutical Research  
Division of Warner-Lambert Company  
Attention: Robin Pitts, R.Ph.  
Sr. Manager, FDA Liaison, Worldwide Regulatory Affairs  
2800 Plymouth Road, P.O. Box 1047  
Ann Arbor, MI 48106-1047

→ NOTE: Subsequent  
pre-NDA meeting held  
on July 17, 2002  
minutes were not  
written

Dear Ms. Pitts:

Please refer to the meeting between representatives of your firm and FDA on June 7, 2000. The purpose of the meeting was to discuss the structure, format, and presentation of data for the pregabalin New Drug Application (NDA).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

*{See appended electronic signature page}*

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

## MEETING MINUTES

Meeting Date: June 7, 2000      Time: 10:00 - 11:30      Location: WOC II

IND: — 53,763      Meeting request date: 3/17/00

Drug: Pregabalin      Date sponsor requested: May/June 2000

Sponsor: Parke-Davis Pharmaceutical Research      Briefing document submission: 5/5/00

Type of Meeting: Pre-NDA Meeting

### Food and Drug Administration:

Russ Katz, M.D.	Division Director, DNDP
Karen Midthun, M.D.	Division Director, DAAODP
Christina Fang, M.D.	Medical Officer, DAAODP
Chang Lee, M.D.	Medical Officer, DAAODP
Len Kapcala, M.D.	Medical Officer, DNDP
Judy Racoosin, M.D.	Medical Officer, DNDP
John Feeney, M.D.	Neurology Team Leader, DNDP
Armando Oliva, M.D.	Medical Officer, DNDP
Philip Sheridan, M.D.	Medical Officer, DNDP
Kun Jin, Ph.D.	Biometrics Team Leader, HFD-710
Kallapra Koti, Ph.D.	Biometrics, HFD-710
Glenna Fitzgerald Ph.D.	Pharmacology Supervisor, DNDP
Stan Lin, Ph.D.	Biometrics, HFD-725
Ray Baweja, Ph.D.	Team Leader, PK, DNDP
Joga Gobburu, Ph.D.	Biopharm, HFD-860
Vanitha Sekar, Ph.D.	Biopharm, HFD-860
Jerry Fetterly, Ph.D.	Biopharm, HFD-860
Dennis Bashaw, Ph.D.	Team Leader, PK, DAAODP
Linda Carter	ADRA, ODE I
Susan Wilson, DVM, Ph.D.	Pharmacology, DAAODP
Robert Osterberg, Ph.D.	Acting Pharmacology Team Leader, DAAODP
Sandra Cook	Project Manager, DAAODP
Jackie Ware, Pharm.D.	Project Manager, DNDP
Ed Fisher, Ph.D.	Pharmacology, DNDP

### Parke-Davis:

Mark Pierce, MD, PhD      Clinical Research

Betsy Garofalo, MD	Clinical Research
Lloyd Knapp, PharmD	Clinical Research
Mitch Brigell, Ph.D.	Clinical Research
Ed Posvar, M.D.	Clinical Pharmacology
Linda LaMoreaux, MPH	Biometrics
Noel Mohberg, Ph.D.	Biometrics
Howard Bockbrader, PhD	Pharmacokinetics, Dynamics, & Metabolism
Zbigniew Wojcinski, DVM, DVSc	Toxicology
Mi Dong	Drug Development
Jan Turner, RN	Regulatory
Byron Scott, R.Ph.	Regulatory
Robin Pitts, R.Ph.	Regulatory
Pauline Kim	Scientific Information Engineering

**Meeting Objective:**

The objective is to discuss the structure, format, and presentation of data for the NDA, which is scheduled to be submitted December 2000.

**Regulatory Status:**

There are currently 3 active INDs for Pregabalin (CI-1008) capsules. The targeted date for the first pregabalin NDA submission is December 2000. This NDA will be for the following indications:

- management of neuropathic pain or management of pain associated with diabetic neuropathy; and

- *⊂*
- *⊂*            *7*
- *⊂*
- *⊂*

**NDA Proposals and Issues for Discussion**

**Note:** Parke-Davis questions are identified by bold typeface. FDA responses are in italics.

**General**

1. Indication-Pain

**Is our clinical plan to support an indication for management of neuropathic pain or management of pain associated with diabetic neuropathy as outlined in Attachment 1B acceptable for filing?**

The proposed plan is acceptable. The issue of how the indication for neuropathic pain would be labeled will be a topic for the advisory committee. In addition, we have the following comments:

Data Issues:

- Duration of treatment is short (< 12 weeks) in the three diabetic neuropathy studies. The durability of the study drug's effect is an important factor in the assessment of efficacy in clinical studies. The 8-week study should be submitted in addition to the 5- and 6-week studies.
- Total diabetic patient exposure (to the dose 600 mg/day) may not meet ICH requirements. FDA prefers the safety database to contain patients using the highest recommended dose or heavily weighted toward patients using the highest recommended dose.

Efficacy Analyses

- Requested Additional Analyses:
  - Longitudinal analysis or area-under-curve method of the pain scale
  - Analysis of allodynia (or other measures of change in skin sensitivity) for patients with the symptom.
  - Rescue medication uses, including amount, time, frequency and types.
  - Analyses of SF-36 health related quality of life and Profile of Mood States (POMS)
  - Subset analyses: pain scores after removing patients who reported somnolence and dizziness

2. Indication- [ ]

[ ]

3. Submission of One NDA

- Is our proposal to request a single review across Divisions acceptable?**  
*An inter-Divisional review is planned. Specific review assignments will be determined at the filing meeting.*
- Is our plan to submit one NDA acceptable, or will the Agency assign a second NDA number to one of the indications for administrative purposes?**  
*Submission of one NDA is acceptable; however, it will be administratively split with two separate NDA numbers.*
- If the Agency assigns a second NDA number to one of the indications, will all correspondence go to both NDAs?**

Yes.

- d. If the Agency assigns a second NDA number to one of the indications, will the Agency withdraw the administrative NDA once the application is approved?  
*We can not answer at this time.*

#### 4. Financial Disclosure Questionnaires

*We note that Linda Carter [email dated May 22, 2000] provided feedback on your financial disclosure plans.*

#### 5. Electronic Regulatory Submission

Is our ERS plan acceptable?

*We note an email from Randy Levin on May 20, 2000, provided his comments regarding the ERS. In addition, we request the following:*

- *Each patient/subject should have a single, unique patient identification number across all data sets (i.e., a patient who goes from a controlled trial into an extension should keep the original patient identification number assigned in the controlled portion). At a minimum, a column could be added to each dataset indicating the patient's previous identification number.*
- *When creating patient identification numbers, use consistent formatting across all datasets.*
- *Include complete labels and codes for the data definition files (see example in section IV.K.Item 11.3 of the Guidance for Industry: Providing Regulatory Submissions in Electronic Format). Supplying the PROC CONTENTS in place of the data definition file (define.pdf) is not adequate.*
- *It would be very useful if you could provide the SAS programs and a list of variables with the submission. A define.pdf file should be provided for statistics as well.*

#### **ITEM 5. Nonclinical Pharmacology and Toxicology**

**At this time we do not have any issues to discuss; however, we would appreciate any comments that the Division may have regarding the content and format of Item 5.**

*Please provide animal line listings.*

*In addition, please note that we will be closely reviewing the data submitted on hemangiosarcomas and will evaluate the risk/benefit ratio. These findings could have significant impact on approvability of the application. The outcome of this review may have profound effects on the entire application*

*Parke-Davis noted that the final preclinical study reports on hemangiosarcomas would be submitted to the INDs in the very near future.*

**ITEM 6, Human Pharmacokinetics and Bioavailability**

6.

- a. Does the Division agree that, based on the draft Biopharmaceutical Classification System, pregabalin is a Class I compound (high solubility/high permeability)?
- b. Does the Division agree that at a given strength and series (family of compositionally proportional formulations), the quality control dissolution data adequately confirm bioequivalence across formulations?
- c. Does the Division agree that the pregabalin dissolution data demonstrate that all immediate release formulations used in clinical trials are rapidly dissolving [  $\bar{X}$ , dissolved in 30 min)?
- d. Does the Division agree that comparisons of dissolution profiles of representative formulations demonstrate bioequivalence of all clinical formulations? For example: the low and high strength (25- and 150-mg) formulations of Series A and the low and high strength (75- and 300-mg) formulations of Series C are bioequivalent to 100-mg Series B formulation?

*Assuming that the draft BCS guidance does not change, we agree with these proposals, based on review of the supporting data that has been submitted with this package.*

7. **Is our population pharmacokinetic analysis plan acceptable?**

*The proposal as described in the meeting package appears acceptable; however, specific details have not been provided.*

*Parke-Davis stated that they are following the FDA population pharmacokinetic guidance.*

8. **Is our plan to evaluate special patient populations and potential drug-drug interactions acceptable?**

*Special patient populations:*

*Please provide a justification, within the NDA submission, for not conducting a hepatic impairment study.*

*Drug-drug interactions:*

☐ *For the neuropathic pain indication, commitments for additional work may be requested, possibly as a phase IV commitment.*

{

9. Does the Division have any comments on the content and format of the PK/PD analysis?

a. Provide rationale for use of average concentration versus other measures of exposure.

b. Please provide a rationale for ☐

c. The model on page 296 does not have a placebo effect. Consider incorporating a placebo-effect in the pharmacodynamic modeling exercise.

d. ☐

e. The ERS (page 333) should include model code and output listing for the first and last models.

**ITEM 8 AND ITEM 10; Clinical and Statistical**

10. Is our outline of the ISE for both indications acceptable?

*Please see question 1 for comments.*

11.

a. In addition to providing summaries of safety data from the controlled studies supporting the neuropathic pain and epilepsy claims, we will also pool data from all controlled and uncontrolled studies across all 3 therapy areas (pain, epilepsy, ☐ ☐ Summaries of pooled data will include demographics, exposure to pregabalin, and the frequency of all and associated adverse events (by body system and by decreasing frequency).

In these summaries, is it acceptable that data from the controlled ☐ ☐ pain studies will be included with the data from all other clinical studies despite the short duration?

The safety data from the acute and chronic studies should be summarized and presented separately. The data for each indication (diabetic neuropathic pain, [ ] epilepsy, [ ] should be summarized and presented separately, as well. Within each indication, controlled trials and extension trials should be summarized and presented separately, by indication, in addition to being pooled into one group.

Parke-Davis asked if the [ ] studies could be pooled. FDA advised that it was acceptable to pool open-label [ ] safety data. FDA also asked for the data to be separated out into single-dose and multiple-dose categories.

For labeling presentation of adverse events, FDA stated that they may or may not have a joint "laundry list" of events; however, for clinical trial adverse event data, two separate safety presentations should be made.

- b. Various investigator terms from our studies code to the preferred COSTART term "Thinking Abnormal". We plan to review those terms in order to determine whether they can be classified into several subgroupings defined by more descriptive clinical terms that might be more informative for use in data summarization and possibly labeling. Is our plan acceptable?

Your proposal is acceptable, assuming source documents (e.g. physician descriptions from CRFs) are reviewed when creating the descriptive clinical term. FDA requested that Parke-Davis also provide a dictionary of terms.

- c. Is our plan to summarize the data from our on-going open-label studies in our ISS and not provide separate research reports for these ongoing studies acceptable?

In addition to being summarized in the ISS, open label studies should be described in individual study reports. These study reports may be "abbreviated" in the sense that efficacy data may not be complete. However, all safety data up to the study cut-off date should be summarized and presented.

- d. Are the following age categories for data summarization acceptable:

- Neuropathic Pain age categories:  $\geq 18$  to  $< 65$ ;  $\geq 65$  to  $< 75$ ;  $\geq 75$ ;

- [ ]

]

The proposal is acceptable.

Neuropharm comments/questions on the ISS:

*Where in the electronic submission will the narratives for deaths, withdrawals due to AEs, and serious AEs be located? This should be marked clearly in the index for the ISS or clinical study reports.*

*On p. 167, in Table 6 "Overview of AEs" for the clinical pharmacology studies, "associated" AEs are to be summarized. What is the definition of "associated"?*

*Parke-Davis stated that the definition of associated was based on the investigator's designation. FDA advised that "associated" events should NOT be the focus of the the ISS. Parke-Davis agreed that it was not; their focus would be on all adverse events.*

*On pp. 168-9, clinical laboratory results and ECG results will focus on clinically significant "drug-related" abnormalities; how was drug-relatedness determined? All clinically significant abnormalities should be described whether or not they are "drug-related".*

*On p. 184, in Table 14 "Listing of Deaths" there are columns for the day of pregabalin the AE began, and the day of pregabalin the patient died. If the patient discontinued from the study treatment after the AE began, how will the time off drug prior to death be indicated? Also, will all deaths be included in the table, or only those occurring within a certain number of days after the last dose of study drug (e.g., 30 or 60)?*

*Parke-Davis stated that all deaths will be included. FDA requested that information be included on patient follow-up, laboratory values, and when the death occurred, and a methodology section describing how follow up was accomplished should also be included.*

*The appendices describing adverse events leading to discontinuation and serious adverse events should be broken down by study indication (e.g. epilepsy, pain, and psychiatry).*

*In appendix 15 describing the abnormal and very abnormal high and low laboratory values, please also include the normal range.*

*How will the QT length be measured, by the central reader or by machine?*

*Parke-Davis stated that QT length would be measured by hand. What method will be used to correct the QT length for heart rate? We will attach our recommended method for standardizing the QT length. FDA does not prefer to use Bizet's correction method.*

*In appendix 18, if a patient discontinues prematurely, is the last on-study laboratory value used for the termination value? How are patients handled who don't have baseline values?*

For studies that included BID and TID dosing regimens with the same total dose  
[ ] please compare the common AE profiles of those groups.

Anti-inflammatory comments on safety:

- Requested Additional Analyses:
  - *Subset Analyses: The safety outcome analysis for diabetic neuropathic pain patients should include:*
    - blood pressure control, including change of drug regimen and doses
    - change in creatinine clearance (if available)
    - change in urinary albumin excretion (if available),
    - doubling of serum creatinine and
    - Symptomatic cardiac events.
  - *Summary Table: Analysis of treatment-limiting AE (separate out dropouts due to AEs for diabetic neuropathy)*
  - *Significant changes over time (i.e. clinical scoring system) of clinical neurological evaluation on nerve function*
  - *CRFs: should include deaths, withdrawals and serious AEs for diabetic neuropathic pain studies*

12. An analysis plan for evaluation of our ophthalmologic safety data was previously submitted on March 1, 2000.

*Comments were provided via fax on 6/5/00, from Dr. Wiley Chambers. In addition, FDA stated that based on our experience with other drugs that have visual field problems, most patients seem to be asymptomatic. Consequently, the firm should not take much reassurance that events were not reported.*

*Parke Davis and FDA agreed to plan a separate meeting to clarify the analysis plan for evaluation of ophthalmologic safety data.*

- a. **The analysis plan for descriptive ophthalmologic safety data specifies the methods for using 4 sources of data to evaluate the incidence of visual function abnormalities. Additionally, an analysis of the quantitative visual field data is provided in the plan. These analyses will be carried out on the patients who were evaluated in the controlled trials in epilepsy, analgesia [ ]. Is this plan acceptable?**
- b. **The analysis plan for descriptive safety data also specifies our proposal to analyze the visual function adverse events that occur during long-term uncontrolled open label exposure. We propose to examine these data using a hazard analysis that shows the rate of events as a function of length of exposure to pregabalin (i.e. number of events occurring within a time interval divided by the number of patients exposed for this interval excluding patients with previous**

events). The interpretation of this analysis will be done with reference to historical or other appropriate controls as well as to data from compounds with known retinal toxicity. Is this approach to the long-term uncontrolled data acceptable?

13. Does the Agency have any comments with regard to our statistical analysis plans?

*FDA has the following comments:*

- [ ]
- [ ]

**ITEM 11, Case Report Form Tabulations**

14. Case report form tabulations will be provided for all controlled and uncontrolled studies, including clinical pharmacology studies, for all exposures at the time of submission. As described in our attached ERS plan, SAS transport files will be provided for the domain profiles. An example of the datasets and variables from our CRF tabulations is provided in Attachment 12.

a. Is this acceptable?

*At this time it can not be determined if the datasets and variables from the case report tabulations are acceptable because many of the variable names were inadequately labeled and explained in the PROC CONTENTS print-out. All abbreviations need to be explained.*

*Also, please explain your statement on page 339 (section 2.10) "Treatment values will only be stored in the demographics dataset." What do you mean by "treatment values"? If this means the subject's randomization group, that variable must be included in all datasets.*

*Additionally, please try to keep the datasets under the maximum size recommended in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format.*

*A few specific comments can be made:*

- *Any adverse event dataset should include the investigator's verbatim term for the AE, the preferred term for the AE, and the system organ class (SOC).*



cc: IND —  
IND 53,763  
HFD-120/Div. File  
HFD-550/Div File  
HFD-550/Midthun  
HFD-120/Katz  
HFD-120/Feeney  
HFD-120/Kapcala/Racoosin  
HFD-120/Oliva/Sheridan  
HFD-550/Fang/Lee  
HFD-120/Fitzgerald/Fisher  
HFD-550/Wilson/Osterberg  
HFD-120/Ware  
HFD-550/Cook  
HFD-550/Lvaccari  
HFD-710/Jin/Koti  
HFD-725/Lin  
HFD-860/Baweja/Gobbura  
HFD-860/Sekar/Fetterly  
HFD-880/Bashaw

**MEETING MINUTES**

/s/

-----  
Jackie Ware

1/19/01 12:16:24 PM

Sandra Cook, Project Manager in DAAODP, signed these official minutes on the original paper copy.

Russell Katz

1/23/01 07:53:07 AM

Dr. Karen Mithun, Director of DAAODP, signed the official minutes on the original paper copy on 8/31/00.

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

5/18/01 01:39:09 PM

Signed for John S. Purvis

550-D10  
EOP2  
June 17, 1999

MEETING MINUTES

IND 53,763

Date: June 17, 1999

Sponsor: Parke-Davis

**Parke-Davis Participants:**

Robert Allen, M.D., Clinical Research  
Mark Pierce, M.D., Ph.D., Clinical Research  
R. Mike Poole, M.D., Clinical Research  
James Strand, Pharm.D., Clinical Pharmacology  
Mohan Beltangady, Ph.D., Biometrics  
Linda LaMoreaux, MPH, Biometrics  
Howard Bockbrader, Ph.D., Pharmacokinetics  
Zbigniew Wojcinski, DVM, DVSc, Toxicology  
Toni Hoover, PH.D., Drug Development  
Irwin Martin, Ph.D., Regulatory Affairs  
Robin Pitts, R.Ph., Regulatory Affairs  
Jan Turner, RN, Regulatory Affairs

**FDA Participants:**

Robert J. DeLap, M.D., Director, ODE V  
John E. Hyde, Ph.D., M.D., Deputy Director, HFD-550  
Sandra Cook, Project Manager  
E. Dennis Bashaw, Pharm.D., Team Leader, Biopharmaceutics  
Chandra Sahajwalla, Ph.D., Team Leader, Biopharmaceutics

Parke-Davis requested an end of phase II meeting to discuss their development plan for phase III.

**Question 1**

Does one positive study in a neuropathic pain model (e.g., diabetic neuropathy)

constitute the "replicated substantiation of efficacy" necessary

Please indicate whether or not we would need to replicate efficacy

FDA would prefer at least one of the models to be replicated.

For diabetic neuropathy we would like to have evidence that the benefit is not attributable to accelerated nerve damage, for example, nerve conduction studies or measuring re-emergence of pain to baseline.

Question 2

FDA will need to review the results before making a determination on approvability.

in addition to the replicated neuropathic model.

The clinical studies section will describe what pain models were used. The indication will be based on studies you select.

Question 3

Are the anticipated total number of patients treated with pregabalin for analgesia acceptable for safety, including the number of patients treated for at least 6 months (1100) and the number of patients treated for at least one year (750)?

The proposed number of patients for the safety database appears to be acceptable. FDA requires the ICH number of patients treated for analgesia at or above the highest recommended dose for safety data.

Question 4

The clinical studies section would reflect the relevant, successful studies.

Question 5

Are the following pain models acceptable to support indication: diabetic neuropathy, post-herpetic neuralgia,

Diabetic neuropathy/Post herpetic neuralgia - these models are acceptable; at least one should be replicated

[ ]

< ]

**Question 6**

a) [ ]

It will depend upon the results and the trial design.

b) [ ]

Yes.

**Question 7**

[ ]

[ ]

**Question 8**

**Is it possible to have one primary reviewer for the safety database, since we may have three simultaneous pending NDAs at the FDA for the same new chemical entity?**

The Divisions have agreed on the goal of single review. The data needs to be presented consistently across applications in modular fashion to facilitate team review.

#### Question 9

In response to 21 CFR: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, we would like to confirm with the Division our Pediatric Plan to defer the submission of pediatric data until after our adult NDA for [ ] is approved. We would also like to request a waiver for collection of safety, efficacy, and pharmacokinetic data in neonates and infants.

We would need to review a proposal for waiver. We cannot comment on the requirements for pediatric studies [ ]

#### Question 10

**Is it acceptable to market pregabalin with 2 distinct trade names?**

CDER does not generally encourage multiple tradenames, as it may lead to medication errors. Justification will be needed.

#### Question 11

**Is our plan to assess abuse liability (both clinically and preclinically) adequate?**

The pre-clinical protocols have not been submitted and we can not comment at this time. Parke-Davis commented that the abuse liability data will not be available at time of submission and they plan to submit at the 120 day safety update.

#### Question 12

**Does the Agency have any comments on our proposed cross-referencing strategy?**

Please submit full archival copies for each NDA. The number of desk copies can be negotiated. Suggest submitting electronic documents in lieu of paper desk copies.

#### Question 13

**Are there additional comments on our development plan?**

There are no additional comments at this time.

### Biopharmaceutics Questions

#### Question 1

**Are the studies defined in the clinical pharmacology/pharmacokinetic plan acceptable for submission and that the approach of using similar documents for the pain, epilepsy, [ ] submissions is acceptable?**

The proposed studies are acceptable from the \_\_\_\_\_ standpoint. [

Please also submit any pharmacokinetic data that was generated from the Phase 3 efficacy trials if it was available. The sponsor should also look for any pharmacokinetic/pharmacodynamic relationships within this data.

**Question 2**

**We would like to confirm that 1) we have achieved the requirements for a Class I agent based on the BCS draft guidance and 2) that we have sufficient information to support a waiver requesting exemption from performing a bioavailability/bioequivalence study. We would also like to discuss what guidance the Division can provide in our preparation of the waiver request.**

The Class I BCS draft guidance is a draft only and is not final at this time. The FDA cannot provide comments/instructions on the use of a draft guidance as it may be changed at any time. Use of this guidance in its current form is at your own risk, as the guidance may not be adopted or may be adopted in a changed form.

At the present time, the sponsor does not appear to have grounds for a waiver request to be granted.

Sandra N Cook  
Project Manager

Concurrence Chair:

Robert J DeLap 04/17/00  
Director, ODE V

- cc:
- IND 53,763
- HFD-550/Div. File
- HFD-550/Cook
- HFD-550/Fang/Midthun
- HFD-550/Villalba
- HFD-880/Bashaw
- HFD-105/DeLap

**MEETING MINUTES**