CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-723

Administrative/Correspondence Reviews

NDA 21-723, pregabalin

Additional information pertaining to this section can be found in the action package for NDA 21-446.

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™ (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).

Department of Health and Human Services
Food and Drug Administration

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

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

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

NDA NUMBER
21-446

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)	STRENGTH(S)
Pregabalin s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid	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	b. Issue Date of Patent	c. Expiration Date of Patent
6,197,819	3/6/2001	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	FAX Number *(if available)*
60201-3135	847-491-3625
Telephone Number	**E-Mail Address *(if available)***
847-491-2105	

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)

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? ☐ 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)*

Karen DeBenedictis

Date Signed: 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

Department of Health and Human Services
Food and Drug Administration

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

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

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

NDA NUMBER
21-446

NAME OF APPLICANT / NDA HOLDER
Parke-Davis, Division of Pfizer Inc

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TRADE NAME (OR PROPOSED TRADE NAME)
Lyrica

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pregabalin s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid	25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg

DOSAGE FORM
Oral Capsules

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

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,563,175	10/8/1996	10/8/2013

d. Name of Patent Owner	Address *(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 2nd 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	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. 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.)* 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)*	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?		
1 (one)		☒ 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.***

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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)*

Karen DeBenedictis

Date Signed: 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

Department of Health and Human Services
Food and Drug Administration

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

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

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

NDA NUMBER
21-446

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)	STRENGTH(S)
Pregabalin s-(+)-4-amino-3-(2-methylpropyl)-butanoic acid	25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg

DOSAGE FORM
Oral Capsules

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,001,876	12/14/1999	7/16/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Warner-Lambert Company LLC Attn: Charles Ashbrook, Esq. 2800 Plymouth Road Ann Arbor, Michigan 48105	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. 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.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

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

The proposed labeling states, in the "Indications and Usage Section", that pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and herpes zoster (post herpetic neuralgia) in adults.

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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Karen DeBenedictis

Date Signed: 10/28/03

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☐ 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

Department of Health and Human Services
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Oral Capsules

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6,117,906	10/8/1996	11/27/2010

d. Name of Patent Owner	Address *(of Patent Owner)*	
Warner-Lambert Company LLC (see address, phone, fax to right) Attn: Charles Ashbrook, Esq. 2800 Plymouth Road Ann Arbor, Michigan 48105 2nd Patent Owner Northwestern University Attn: Dr. Indrani Mukharji Director, Department of Technology Transfer 1880 Oak Avenue, Suite 100 Evanston, Illinois 60201-3135 847-491-2105 fax=847-491-3625	201 Tabor Road City/State Morris Plains, New Jersey ZIP Code 07950 Telephone Number 734-622-5215	FAX Number *(if available)* 734-622-1553 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.)*	
☞ N/A	City/State ZIP Code Telephone Number	FAX Number *(if available)* 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

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

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™ (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).

NDA 21-723, pregabalin

Additional information pertaining to this section can be found in the action package for NDA 21-446.

NDA 21-446

LYRICA (pregabalin) Capsules

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(l)]

Pfizer 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.

Signature of Company Representative

Date 9/30/03

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

DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

DATE:	August 31, 2004
DRUG:	LYRICA (pregabalin) 25, 50, 75, 100, 150, 200, 225 and 300 mg Capsules
NDA:	21-723
NDA Code:	Type 1S NDA
SPONSOR:	Pfizer, Inc.
INDICATION:	For the management of post-herpetic neuralgia

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 reviewed the application for pain due to diabetic peripheral sensorimotor neuropathy (DPN) on a priority clock and found that application to be approvable. The Division of Neuropharmacological Drug Products is reviewing the applications for epilepsy and GAD.

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 Joan Buenconsejo, M.S. 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 three studies (1008-045, 1008-127 and 1008-196) in support of efficacy. An additional study, 1008-030, failed to show a difference between pregabalin 75 or 150 mg/day and placebo; and a fifth study, 1008-132, was prematurely terminated due to the imposition of clinical hold on the IND. A detailed review of these studies and of the safety of the product was performed by Mwango 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 (DNDP), 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. Review of the epilepsy and GAD applications are ongoing in the DNDP.

Efficacy:

The three pivotal studies were similar in design. Subjects were adults with post-herpetic neuralgia who had pain lasting at least three months after the zoster rash had healed, except for Study 045, which required pain lasting six months after healing of the rash. Subjects were required to have a minimum score of 40 mm on the Visual Analogue Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) and a score of at least 4 on the Likert pain rating scale (a numerical rating scale from 0 {"no pain"} to 10 {"worst possible pain"}). Creatinine clearance of greater than or equal to 30 mL/min was also required. Patients were excluded if they had not been responsive to gabapentin. Each study employed a one-week forced-titration period and a fixed-dosing period of 7 weeks in Studies 045 and 127, and 12 weeks in Study 196. Patients who were unable to tolerate study drug were discontinued. The subjects were required to complete daily diaries of pain ratings.

The primary efficacy outcome for all three studies was the final (endpoint) weekly mean pain score, defined as the mean of the last 7 diary entries while on study medications. If fewer than 7 entries were recorded, the available scores were used to determine a mean. This design essentially represents a Last Observation Carried Forward (LOCF) methodology for the imputation of missing data. This technique for assessing missing data has been demonstrated to overestimate the benefit of drugs used to treat chronic pain. Due to these concerns, the Division requested that the sponsor reanalyze the data employing a more conservative Baseline Observation Carried Forward (BOCF)

methodology for the imputation of missing data. However, the sponsor's analyses required that the subjects complete all visits, but not the entire treatment period. Thus, some subjects termed "completers" did not complete a full 8 or 13 weeks of treatment. Therefore, Drs. Kashoki and Buenconsejo employed a more appropriate methodology in their reanalyses. They redefined the study endpoint as the prespecified last week of treatment with study medication, Week 8 or 13 depending on study, and considered subjects who withdrew before endpoint as non-completers. In addition, for patients who did not prematurely withdraw from the study, they used the average of available data from the last available week on treatment to carry forward for their analyses.

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
- Either The Profile of Mood States (POMS) or the Zung Self-rating Depression Scale.

Study 1008-045 (045) was a multicenter (in Europe and Australia), randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 50 mg TID or 100 mg TID and placebo.

Two hundred thirty-eight subjects were randomized. Forty-six subjects did not complete the study. See Dr. Kashoki's Table 6.3.4.6 for a breakdown of subject disposition.

The sponsor's analyses of the primary efficacy outcome data documented statistically significant treatment effects for both the 150-mg/d and the 300-mg/d dose compared to placebo. Drs. Kashoki and Buenconsejo's analysis confirmed these results.

Study 1009-0045 Endpoint mean pain scores: Results of ANCOVA with BOCF

		Treatment comparisons

				(Pregabalin - Placebo)			
Treatment	N	Least Squares Means	SE	Difference	95% CI	Un-adjusted p-value	Adjusted p-value
Placebo	81	6.32	0.22				
Pregabalin 150	81	5.20	0.21	-1.12	(-1.718-0.522)	0.0003	0.0004
Pregabalin 300	76	5.21	0.22	-1.11	(-1.723-0.502)	0.0004	0.0004
SE = Standard error; CI = Confidence interval							
Endpoint = Last 7 available scores while on study medication, up to and including day after last dose							
Adjustment based on Hochberg's procedure							

(Applicant's Table E1, Appendix D.23, RR 720-04356, 1008-045, P. 1889)

The review team undertook an exploration of the impact of creatinine clearance on efficacy based on a similar exploration by the sponsor in the other studies in this application and in the DPN application. Clear differences in tolerability were apparent between strata defined as Low (creatinine clearance between 30 and 60 mL/min) and Normal (creatinine clearance greater than 60 mL/min).

Study 1008-045 Patient Disposition by Creatinine Clearance Strata

Disposition	Treatment Group				
	PLB	PGB 150-L	PGB 150-N	PGB 300-L	PGB 300-N
Randomized	81	42	39	45	31
ITT	81	42	39	45	31
Completed Study	61	36	35	30	30
Withdrawn:					
Adverse Event	8 (10%)	6 (14%)	3 (8%)	12 (27%)	0 (0%)
Lack of Compliance	2 (25%)	0	0	0	1 (3%)
Lack of Efficacy	7 (9%)	0	0	1 (2%)	0
Consent withdrawn	3 (4%)	0	1 (3%)	2 (4%)	0

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 both the 300 mg/d Normal creatinine and the 150 mg/d Low creatinine groups, by both the sponsor's and the Division's methodologies for imputing lost data. However, the results for the 150 mg/d Normal creatinine group did not achieve statistical significance in the Division's analysis, possibly due to the small sample size as the study was not powered for these subset analyses.

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

Study 1008-127 (127) was a multicenter (U.S.), randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 100 mg TID (for subjects with

creatinine clearances less than or equal to 60 mL/min) or 200 mg TID (for subjects with creatinine clearances greater than 60 mL/min) and placebo.

One hundred seventy-three subjects were randomized. Forty-one subjects did not complete the study. See Dr. Kashoki's Table 6.3.2.16 for a breakdown of subject disposition.

The sponsor's analyses of the primary efficacy outcome data documented a statistically significant treatment effect for the pooled pregabalin dose groups compared to placebo. Drs. Kashoki and Buenconsejo's analysis separated the dose groups and found a statistically significant treatment effect for the 600-mg/d group compared to placebo. The treatment effect did not achieve statistical significance in the 300-mg/d group, again possibly due to the small sample size in this subset analysis, for which the study was not powered. Also, there was a high drop out rate in this group resulting in a low number of patients for this efficacy analysis.

Table 6.3.2.24.c: Reviewer's analysis: Change in mean pain scores at Week 8 and Endpoint, ANCOVA[1] (BOCF) – Protocol 127

	Placebo	Pregabalin 300/600	Pregabalin 300	Pregabalin 600
Baseline[2]	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Endpoint[3]	5.25 (2.5)	4.42 (2.4)	4.76 (2.4)	4.24 (2.4)
Change[4]	1.18 (1.9)	1.87 (2.2)	1.84 (2.6)	1.89 (2.1)
LS means	1.21 (0.2)	1.93	1.75 (0.4)	2.00 (0.3)
p-value[5]		0.0137	0.2346	0.0302
Week 8[6]	5.20 (2.6)	4.42 (2.4)	4.85 (2.5)	4.21 (2.4)
Change[7]	1.25 (1.9)	1.85 (2.2)	1.74 (2.6)	1.90 (2.1)
LS means	1.28 (0.2)	1.96	1.73 (0.4)	2.07 (0.3)
p-value[5]		0.0224	0.3334	0.0333

[1] Analysis includes treatment, center, and creatinine clearance strata (for pregabalin 300/600 only group) as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment.
[2] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers
[4] Change= Baseline – Endpoint

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 sponsor's results were consistent with the primary analysis, documenting a statistically significant difference from placebo for the combined treatment groups. However, the review teams analysis, separating the dose groups and using the more conservative BOCF definition, found that only the 600-mg/d group showed a statistically significant difference from the placebo group.

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

Study 1008-196 (196) was a multicenter (Europe and Australia), randomized, placebo-controlled, double-blind, parallel-group study comparing pregabalin 75 mg BID, 150 mg

BID or 300 mg BID and placebo. There were 4 treatment arms: placebo, 150 mg/d, 300 mg/d and 300/600 mg/d. Subjects were stratified to treatment dose on the basis of creatinine clearance. Subjects in the 300/600 mg/d group who had a creatinine clearance of less than 60 mL/min were treated with 300 mg/d, and subjects with a creatinine clearance greather than 60 mL/min were treated with 600 mg/d.. The sponsor analyzed all subjects in the 300/600 mg/d treatment arm together as one group.

The review team reassigned patients with creatinine clearances less than 60 mL/min who had been included in both the 300-mg/d and 300/600-mg/d groups into a single Low creatinine clearance 300-mg/d group. They analyzed the subjects in the 300-mg/d group with clearances greater than or equal to 60 mL/min as a Normal creatinine clearance 300-mg/d group; and they analyzed the subjects in the 150-mg/d group as either Low creatinine clearance 150 mg/d or Normal creatinine clearance 150 mg/d based on the same cutoffs. Additionally, several subjects in the 300/600-mg/d group were assigned to the incorrect dose for their creatinine clearance by the sponsor. The review team reassigned these subjects to the correct dose in their analyses.

Three hundred seventy subjects were randomized, but only 368 took at least one dose of study medication. One hundred twenty-six subjects did not complete the study. See Dr. Kashoki's Table 6.3.3.16 for a breakdown of subject disposition.

The sponsor's analyses of the primary efficacy outcome data documented statistically significant treatment effects for the each of the pregabalin dose groups (150 mg/d, 300 mg/d and 300/600 mg/d) compared to placebo. Drs. Kashoki and Buenconsejo's analysis found statistically significant treatment effects only for the 150-mg/d Normal and the 600-mg/d groups compared to placebo. While the treatment effect did not achieve statistical significance in the 150-mg/d Low or the 300-mg/d Low and Normal groups, it should be noted that the trial was not powered for these post-hoc subgroup analyses.

The reviewers also analyzed the results at Week 8, for ease of comparison with the results from the other two pivotal trials, and to assess efficacy for the standard period required by the Agency for PHN efficacy trials. The results of this analysis revealed statistically significant treatment effects for all of the groups compared to placebo except for the 150-mg/d Low group.

Study 1008-196 Reviewer's analysis: ANCOVA, mean pain score at Endpoint (BOCF) –

Treatment	N	Baseline Mean	Least-Squares	SE	Treatment Comparisons (Pregabalin – Placebo)

			Mean				
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.19	0.22			
PGB 150							
Low[4]	26	6.77	5.76	0.41	-0.43	0.3514	0.3514
Normal[5]	61	6.30	5.12	0.27	-1.07	0.0020	0.0080
PGB 300							
Low[4]	59	6.84	5.38	0.27	-0.81	0.0194	0.0582
Normal[5]	65	6.60	5.54	0.26	-0.65	0.0532	0.1064
PGB 600	64	6.64	4.72	0.26	-1.47	<0.0001	0.0005

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the two pairwise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min

Study 1008-196: Reviewer's analysis: ANCOVA, mean pain score at Week 8 (BOCF)

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.11	0.20			
PGB 150							
Low[4]	26	6.77	5.79	0.38	-0.31	0.4461	0.4461
Normal[5]	61	6.30	5.00	0.25	-1.11	0.0006	0.0024
PGB 300							
Low[4]	59	6.84	5.22	0.26	-0.89	0.0066	0.0174
Normal[5]	65	6.60	5.29	0.24	-0.82	0.0087	0.0174
PGB 600	64	6.64	4.74	0.25	-1.37	<0.0001	0.0005

[1] Week 8= Average of available scores between day 51 to day 57, for subjects who completed that week, and baseline mean pain score for non-completers
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[3]Low = creatinine clearance is between 30 and 60 mL/min
[4]Normal = creatinine clearance >60 mL/min

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 sponsor's results were consistent with their primary analysis, documenting a statistically significant difference from placebo for each of the treatment groups. However, the review teams analysis, stratifying the dose groups and using the more conservative BOCF definition, found that the Low creatinine clearance strata of both the 150-mg/d and 300-mg/d dose groups did not show a statistically significant difference from the placebo group.

The secondary outcome analyses were generally supportive of the findings for the 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 PHN program, a total of 924 patients received at least one dose of pregabalin in controlled trials and 259 subjects participated in uncontrolled trials. 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. In the PHN program, 212 and 48 subjects were exposed to 300 or 600 mg of pregabalin for at least 6 months or 1 year, respectively. Eight PHN subjects were exposed to these doses for at least 2 years.

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 a 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 lead 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, was being treated forpostherpetic neuralgia, and had a history of falls.

Twenty subjects died in the PHN study population. Four deaths were due to cancer, 4 due to pneumonia, 9 due to cardiac adverse events, and 1 each due to gastrointestinal hemorrhage, pancreatic necrosis and pulmonary embolus. Dr. Kashoki's review of the CRFs and narratives for these patients resulted in her conclusion that none of them was clearly associated with pregabalin treatment.

Discontinuations Due to Adverse Events

Approximately 13% of subjects in the controlled-trials overall database and 14% of pregabalin-treated subjects in the controlled-trials PHN database discontinued due to an adverse event.

Dr. Winchell's tables, reproduced below, tabulate the percentages of subjects who withdrew from the three pivotal trials based on dose and creatinine clearance stratum.

Disposition = Withdrawn Due to Adverse Events, CLcr <60 mL/min

	Placebo	PGB 150	PGB 300	
1008-045	8/81 (10%)	6/42 (14%)	12/45 (27%)	
1008-127	4/84 (5%)		11/30 (37%)	
1008-196	5/95 (5%)	5/26 (19%)	13/59 (22%)	
ALL	17/260 (7%)	11/68 (16%)	36/134 (27%)	

Disposition = Withdrawn Due to Adverse Events, CLcr ≥60 mL/min

	Placebo	PGB 150	PGB 300	PGB 600
1008-045	8/81 (10%)	3/39 (8%)	0/31 (0%)	
1008-127	4/84 (5%)			17/59 (29%)
1008-196	5/95 (5%)	2/61 (3%)	7/65 (11%)	14/64 (22%)
ALL	17/260 (7%)	5/100 (5%)	7/96 (7%)	31/123 (25%)

The most common adverse events that resulted in discontinuation from the PHN controlled clinical trials were dizziness, somnolence, confusion, peripheral edema and ataxia. Subjects in the 600-mg/d dose groups had a higher incidence of discontinuations for adverse events and additionally reported facial edema, hallucinations, abnormal gait, vision abnormalities and headache with greater frequency than the other treatment groups.

Serious Adverse Events

Eight percent of pregabalin-treated patients in the overall database experienced one or more serious adverse events. 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%.

No serious adverse event occurred with a frequency of greater than 1% in the pregabalin-treated patients in the controlled PHN trials. The most common serious adverse events in those trials were chest pain, pain, cerebral ischemia, ventricular extrasystoles, pneumonia

and urinary tract infection. One report each of anaphylactoid reaction, cellulitis, facial edema, leukopenia, lung fibrosis, lymphoma-like reaction and peripheral edema occurred in the pregabalin-treated subjects. Based on her review, Dr. Kashoki determined that the cases of lung fibrosis, anaphylactoid reaction and peripheral/facial edema may be suggestive of a relationship to pregabalin treatment.

The most common serious adverse events in the overall PHN database were accidental injury, pneumonia, myocardial infarction, congestive heart failure and syncope. Based on her review, Dr. Kashoki determined that a single case each of pancreatitis, visual field defect and retinal disorder was possibly related to pregabalin exposure.

Common Adverse Events

In the controlled PHN trials, dizziness (26%) and somnolence (16%) were the most common adverse events in pregabalin-treated subjects. Peripheral edema occurred in 12% of the pregabalin-treated subjects. Other common adverse events included ataxia, abnormal gait, incoordination, confusion, abnormal thinking, amnesia, speech disorder, weight gain, infection, blurred vision, diplopia, accidental injury, dry mouth and constipation.

Specific Adverse Events of Concern

For discussion of the following categories of clinical adverse events, the reader is referred to my memo regarding NDA 21-446, dated June 28, 2004, for the DPN indication: Vascular Neoplasms, Dermatopathy, Ophthalmologic Adverse Events, Glycemic Control, Reproductive Toxicity, Edema and Weight Gain, ECG Findings and QT-Interval Changes, Platelet Abnormalities, and Creatinine Kinase Elevation

Non-Clinical Safety, Biopharmaceutics, CMC, Nomenclature and Abuse Liability

Nonclinical Safety, Biopharmaceutics, Chemistry, Manufacturing and Controls, Nomenclature and Abuse Liability, Withdrawal Phenomena and Overdose are also discussed in my memo to NDA 21-446. Some new information was requested by the CSS staff in their assessment of abuse liability and scheduling recommendation. That information was submitted, but without adequate time to allow for review during this cycle. Additional concerns regarding CMC matters were raised in an amendment to the NDA received on August 25, 2004. Those issues have been reviewed and the sponsor's submission renders them approvability issues. They are clearly outlined in the approvable letter.

Discussion:

I concur with the clinical review team that the sponsor has provided substantial evidence of efficacy for pregabalin in the treatment of post-herpetic neuralgia.

Dr. Kashoki has recommended against approval of this application. Her recommendation is based on the adverse event profile seen in the clinical studies, the greater incidence of these events at the higher doses and in subjects with poor renal function (defined as a creatinine clearance rate of less than 60 mL/min in the studies included in this application), and her assessment that the efficacy of the product has only been established for those higher doses based on the review team's post-hoc analyses. Dr. Winchell has recommended approval of this application with dosing recommendations based on the finding that the adverse events attributable to pregabalin appear to be exacerbated in patients with poor renal function.

I agree that this product appears to be associated with adverse events that are of clinical concern, particularly in the PHN population, as this disorder occurs most frequently in older patients. However, while I do think that the data indicate an increasing risk of adverse events associated with increased dose and with decreased renal function, I do not think that the post-hoc analyses performed by the review team can be interpreted as statistically viable due to the probability that these subgroup analyses were not powered to provide statistically reliable results. Therefore, I am convinced that the sponsor has adequately demonstrated efficacy at each of the doses that they studied. I do concur with the clinical review team's recommendation that dosing should be titrated slowly to effect and that the 600-mg dose should only be employed when necessary and when a patient has clearly demonstrated an ability to tolerate lower doses. I also agree that renally impaired patients should only be titrated to the 300-mg dose when necessary and after tolerability has been established at lower doses.

I refer the reader to my memo recommending approval for NDA 21-446 for the DPN indication for discussion of the other clinical and the non-clinical concerns raised by the review team. My conclusions and recommendations regarding these issues are unchanged for this application, including my recommendations for Phase 4 commitments.

[

]

Action recommended by the Division:

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

1. Additional adequate and well-controlled clinical studies to assess the ophthalmologic toxicity of pregabalin

2. [redacted]

3. [redacted]

4. [redacted]

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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/s/

Bob Rappaport
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MEDICAL OFFICER

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Office Director's Sign-Off Memorandum

Date:	Tuesday, August 31, 2004
NDA:	21-723
Sponsor:	Pfizer
Proprietary Name:	LYRICA (Pregabalin) Capsules
From:	Robert J. Meyer, MD Director, ODE II

Introduction: LYRICA contains pregabalin as its active ingredient. Pregabalin is a new molecular entity, a single (S) enantiomer, that is reported to be a gamma-aminobutyric acid (GABA) analogue. It is under development for a number of neurologic and psychiatric indications. While all indications were appropriately submitted together in a single NDA, the indications were administratively split to allow for differing timelines (one indication was a priority review) and differing review responsibilities across divisions and ODEs. This NDA is the second indication for pregabalin being reviewed in Office of Drug Evaluation 2. The first review was a priority and was for diabetic peripheral neuropathy (or DPN). This review was the subject of a prior ODE memo on July 28th, 2004 for NDA 21-446 and an "approvable" action on July 29th, 2004. LYRICA (pregabalin) has not yet been approved in the US for any indication. It is being concurrently reviewed under separate NDA numbers in ODE I (where the indications of general anxiety disorder and epilepsy were reviewed by the Division of Neuropharmacologic Drug Products).

This NDA is for post-herpetic neuralgic pain and it is on its first cycle. If the DPN indication had been approved, this application would have effectively been an efficacy supplement to that NDA, which received a priority designation. Unlike for DPN, there is a medication currently available for the post-herpetic neuralgia indication – Neurontin or gabapentin, and so a priority status was not deemed appropriate for PHN.

The drug moiety in Pregabalin 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. The drug was originally under development by Warner-Lambert and is submitted by Pfizer now that the former has been acquired by the latter. The drug has recently been approved for marketing in the EU.

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 post-herpetic neuralgia, once all details of labeling, scheduling and some minor CMC deficiencies are attended to. 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. While these further data needs were conveyed to the sponsor in the action letter for NDA

21-446 (along with one data need specific to that NDA), the general issues should be reiterated in the action letter for NDA 21-723 as well. There are issues related to labeling and scheduling that will preclude an approval action at this time, however, as they did for the diabetic peripheral neuropathy indication on July 29th, 2004. These issues are also expanded upon later in the memo. Finally, for the sake of completion of the record, this memorandum substantially repeats much of what was in the July 28th memorandum.

CMC: LYRICA capsules are available in multiple dosage strengths: 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules. Those strengths above 100 were not included in the DPN application. There are some minor, but significant CMC issues remaining with pregabalin due to a recently submitted amendment (submitted 8/30/04) and the ONDC recommendation is for an approvable. These issues should be easily resolvable.

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 22nd, 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, particularly for the diabetic indication. This is due to the fact that the diabetic neuropathic population has relatively high incidence and prevalence 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, for what it's worth, rats do not 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 300 or 600 mg per day, in divided doses (either twice daily or 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 Cmax at steady state is approximately 5 mcg/ml at the 300 mg q 8 hour dosing regimen, with a Tmax 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 Cmax and a delayed Tmax 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. Css 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 Cmax, 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 indication was focused on patients with pain due to post-herpetic neuralgia (PHN), defined as persistent pain beyond the zoster rash (either 3 months or 6 months beyond the zoster episode, depending on the study). This population is not unexpectedly quite elder compared to many general indications. Therefore, they may be a more vulnerable population, one where renal impairment may be quite prevalent (and thereby there are implications for the pharmacokinetics of this renally excreted drug) and also one in which there is a fair amount of potential confounding factors in the safety evaluation.

Efficacy: The sponsor performed five main efficacy trials in the PHN population, four of which were completed. The fifth (1008-030) was terminated in response to a clinical hold imposed at the time the hemangiosarcomas in mice were first identified. The

sponsor commendably explored a range of doses and dose regimens in these phase 3 studies. A brief synopsis of the key studies follows. Note that all the studies included some titration period allowing for a lower dose start to be titrated up in the first week as tolerated. For more detail, please see Dr. Kashoki's primary review.

- Study 1008-045 was an 8-week, double-blind study of pregabalin, with either 50 mg TID or 100 mg TID being studied against placebo. It was conducted in foreign sites (the EU and Australia, primarily) in patients at least 6 months out from their zoster episode. In this study, both dose groups were overall found to be effective compared to placebo in terms of improvement in mean pain scores at endpoint (the primary variable). When looked at by % of patients achieving a 50% reduction in their pain scores at baseline as a "responder" definition, that was seen in only 9% of placebo patients, compared with 25% and 21% in pregabalin 50 TID and 100 TID respectively. This study was not designed to examine the effect of creatinine clearance on efficacy (as were other PHN studies) but a post-hoc analysis by the FDA reviewers showed that, in addition to clear intolerance of the medication with decreased renal function, there was an apparent decrement in efficacy as well in this group. That said, it must be remembered that for the purposes of the analyses, dropouts were assumed to have not changed in their pain scores. Also, post-hoc analyses will have less power to detect true treatment differences since they are not planned for in the sample size calculations. When one does a "responder" analysis for a 50% reduction in symptoms based on dose-CrCl, the low dose, low clearance group showed 29%, the low dose, "high" clearance group (i.e., CrCl > 60 mL/min) was 21%, the high dose, low clearance group was 11% and the high dose, high clearance group was 35%. Again, this study was NOT designed to examine effects by baseline creatinine.

- Study 1008-127 examined two doses – 100 mg TID and 200 mg TID in patients at least 3 months out from their zoster episode. The study was based in the US, was 8 weeks in duration and patients were assigned to the dose by CrCl, with those under 60 mL/min getting 100 mg TID and those above 60 mL/min getting 200 mg TID. In the overall analysis of pregabalin vs placebo, the study drug was highly significantly effective, with over 30% of patients in pregabalin having at least a 50% reduction in their pain scores and only 20% of patients in placebo having the same. When separately analyzed by dose/CrCl, the100 mg TID dose was not statistically better than placebo on a responder analysis nor on mean reduction in pain scores at baseline. This is presumably primarily a power issue, however, as the mean scores and percent achieving a 50% reduction in the responder analysis were very similar between 300 and 600 mg daily doses and clearly numerically different from placebo.

- Study 1008-196 examined doses of 75, 150 and 300 mg twice daily in patients with at least 6-months of pain beyond their zoster episode. It was largely a European and Australian-based study. While patients were not strictly assigned to dose by CrCl, those with low CrCl (< 60 mL/min) who were randomized to 600 mg were instead given 300 mg. Those with low CrCl randomized to the other dose-groups got their assigned doses. This is notable because the discontinuation

rate due to adverse events was very much higher in this group compared to the higher CrCl group, irrespective of the dose in question (i.e., the 75 BID or the 150 BID). The drop-out rate for AE in the 75 BID group for the low CrCl individuals was 19%, while it was only 3% in the those with the higher CrCl (with placebo being 5%). In the 150 mg BID group, the rates were 22% low-CrCl and 11% higher-CrCl group. In the 300 mg BID group, all patients had CrCl greater than 60 mL/min and the AE withdrawal rate was 13%. On the overall analyses by dose, there was a statistically significant effect of all three doses in reducing mean pain scores at endpoint. In looking at the breakout by CrCl, the 75 BID, low CrCl group had the least effect numerically, the 300 mg BID dose had the best effect numberically. In an ANCOVA analysis done on mean pain score changes at week 8, all groups were better than placebo except for the 75 mg BID, low CrCl group. This group had a numerical advantage that was fairly small and it was not very different from placebo in the responder-50% analysis (8 vs. 6% for placebo). This may in part be due to confounding by the drop-outs, as the rate was fairly high in this group, but one would expect more exposure for the low CrCl group than the higher CrCl group and therefore one might have expected more efficacy in this low dose group. While that trend was seen at 150 BID, it was not in 75 BID for unclear reasons.

- Study 1008-130 studied relatively low doses (75 and 150 mg total per day) and failed to demonstrate efficacy and study 1008-132 was terminated early.

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 924 patients in the PHN program in controlled trials and 259 in uncontrolled trials. Please see the MO review t for detailed discussions of safety. I will touch only on the notable positives and negatives.

There was only 1 death in the PHN program, without clear causal link to the drug. It was a death due to a head injury sustained in a fall (which could have been due to pregabalin-induced effects like somnolence or dizziness, but this is not ascertainable). There were more withdrawals for AEs in the treated group compared to placebo (12% vs. 7%) with the most frequent AEs leading to withdrawal of patients in the PHN program being dizziness, somnolence, confusion and ataxia. The rate of withdrawal for AEs was higher for the lower CrCl patients than those with CrCl over 60 mL/min, irrespective of dosing, such that the rate for 300 mg daily for the low group exceeded the rate with 600 mg daily in the group with more normal renal function. 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 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. Dr. Chambers felt most of the changes to be minor and not likely to impair patient function, and at least for the visual field cuts, further reviews of the data and discussions with the company's eye consultants revealed little clear signal of a drug-related connection. However, Dr. Chambers 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. Given the preclinical findings (which apparently showed some retinal effects of the drug at it highest doses), the priors with vigabatrin and the weak signal in this database – I agree with.

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. While this is of more concern with the diabetic neuropathy indication,, it remains a general labeling issue.

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 post-herpetic neuralgia, once labeling and scheduling has been settled within the FDA and HHS. The most concerning fact in the database is the hemangiosarcomas in mice. While the sponsor did not prove these to be species specific (though they are not found in rats) nor did they prove a mechanism that proves irrelevance to humans, since the drug is non-genotoxic, since the findings were a singles species and since the use of the drug is in primarily an elder population for a finite period of time for the PHN indication, I believe these findings do

not merit a "not approval." Rather, I think a strong statement in the labeling about the carcinogenicity in humans is warranted and physicians and patients can make their own risk assessment based on the known data.

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.

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

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Robert Meyer
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MEDICAL OFFICER

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: [redacted]

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 [redacted]

The original NDA was received 30-OCT-2003

NDA 21-446 is the lead NDA for CMC review for 3 other NDAs for pregabalin:

NDA 21-723 for PHN in HFD-170 (added strengths 150, 200, 225, 300 mg)
And in HFD-120
[redacted]
NDA 21-724 for Epilepsy (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 [redacted] which could be formed during [redacted] 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] 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] for a new method for producing [redacted] Structural alerts for mutagenicity are present for various [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 [redacted] submitted stability data on only pilot scale batches from the R&D site – [redacted] 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 [redacted] 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. Note that the expiry for other strengths for different indications have not been finalized – the firm is requesting 3 yrs, however the CMC review concludes that a [redacted] expiry should be assigned. 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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8/26/04

Malandro, Lisa

From: Malandro, Lisa
Sent: Monday, August 02, 2004 4:45 PM
To: Malandro, Lisa; Ware, Jacqueline H
Subject: FW: NDA 21-723 Pregabalin Information Request

PHN_MS.doc (59 KB)

-----Original Message-----
From: Malandro, Lisa
Sent: Monday, August 02, 2004 4:09 PM
To: 'Parker, Jonathon M (Regulatory Affairs)'
Subject: NDA 21-723 Pregabalin Information Request

Jonathan,
Attached is a request for information from the biopharmaceutics reviewer. Please provide response at your earliest convenience as an electronic amendment to NDA 21-446, 21-723, 21-724 ( ) If you have any questions, please do not hesitate to contact me.
Thanks,
Lisa

Pregabalin Modeling and Simulation for the PHN Indication

COMMENTS:

We have reviewed your proposal on the modeling and simulation analyses to link the BID and TID regimens for the PHN indication. We consider modeling pooled data from different regimens (i.e., TID and BID) not very informative for the stated purpose and we recommend the following alternative approach. We acknowledge that some of the recommended analyses may not be successful due to the small sample size and we will take that into consideration during our evaluation of the analysis results. As an option, you may also explore treating pain scores as a continuous outcome.

RECOMMENDATION:

A. Regarding modeling and simulation:

1. Within the three TID trials, model using pooled data from two trials and predict the remaining trial.
    - Model data from Studies 30 and 45, and predict for study 127.
    - Model data from Studies 30 and 127, and predict for study 45.
    - Model data from Studies 45 and 127, and predict for study 30.

2. Model the three TID trials (Studies 30, 45 and 127) and predict for the BID trial (Study 196).

3. Model the BID trial (Study 196) and predict for each of the three TID trials.

4. Provide data file and codes for final models in electronic format.

B. Regarding presentation of results:

For each simulation scenario, provide the following tables and plots:

Tables

- For each week up to end-of-trial, provide a table showing the observed and predicted % of patients with designated degrees of change in pain score. Express the degree of change in pain score in two ways, one in absolute change in pain score (Table Type 1) and one in % change from baseline score (Table Type 2).

Type 1: Week i

(X) ΔScore >=	% Patients	
	Obs. (Y_1)	Pred. (Y_2)
1	98	97
2	80	75
3	65	62
4	.	

5	.	
6	.	
7	.	
8	.	
9	.	
10	5	1

Type 2: Week i

%Change in pain score (X)	% Patients	
	Obs. (Y_1)	Pred. (Y_2)
≥ 0%	98	100
≥ 12.5%	80	82
≥ 25%	65	70
≥ 37.5%	.	
≥ 50%	.	
≥ 62.5%	.	
≥ 75%	.	

Plots

- Type A plots: X vs. Y1 and Y2 for each week from Week 1 to end-of-trial.
- Type B plots: Y1 vs. Y2 for each week from Week 1 to end-of-trial. For these Type B plots, provide the linear regression statistics for each week.

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/s/

Lisa Malandro
8/3/04 05:16:45 PM

Malandro, Lisa

From: Malandro, Lisa

Sent: Tuesday, July 27, 2004 5:43 PM

To: 'Parker, Jonathon M (Regulatory Affairs)'; Malandro, Lisa

Subject: NDA 21-723 Pregabalin Information Request

Importance: High

Jonathan,
Please provide the following information as an amendment to NDA 21-446, 21-723, 21-724 —

In the same way that you previously analyzed AE frequencies for patients either taking or not taking a PPAR, conduct the following analysis for patients in all controlled trials, and in controlled PHN trials:

Identify patients who took tocopherol (vitamin E). Tabulate the number of patients in each dose group that were taking this medication.

Provide AE tables by dose (including an "all pregabalin") column for the AEs of edema (facial, peripheral, generalized), weight gain, and heart failure. Generate the tables based on each of the following populations:

- PHN patients who took tocopherol

- PHN patients who did not take tocopherol

- All patients in the entire safety database (controlled trials only) who took tocopherol

- All patients in the entire safety database (controlled trials only) who did not take tocopherol

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

Thanks,

Lisa

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/s/

Lisa Malandro
8/3/04 05:19:25 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Wednesday, July 14, 2004 9:10 AM
To: 'Parker, Jonathon M (Regulatory Affairs)'
Cc: Ware, Jacqueline H; Malandro, Lisa
Subject: NDA 21-723 Pregabalin Information Request

Importance: High

Jonathan,
The Division has the following request related to their ongoing review of the PHN application. Please submit your response to this request in electronic archival format as amendments to NDA 21-446, 21-723, 21-724

The Division acknowledges Pfizers attempt to link the TID and BID regimens through modeling and simulations. However, in those analyses, data from both DPN and PHN trials were combined and the posterior check indicated that the 300-mg dose was not well predicted. The Division recommends that Pfizer conduct additional modeling and simulation analyses for the PHN indication as follows:

A. Model the TID trials (Studies 30, 45, 127) to predict the BID outcome for trial 196 at Week 8.
B. Model the BID trial (Study 196) to predict the TID outcome for trials 45 and 127.

Explore modeling by treating the pain score as categorical outcome as well as continuous outcome.

Thanks!
Lisa

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/s/

Lisa Malandro
7/14/04 09:53:59 AM

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
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 ophthamologic 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

Appears This Way
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14 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

ATTACHMENT 2

Appears This Way
On Original

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:

1. *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.*

2. *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	
	1062	772	523	197	769	109							300	600
Clinical	45	35	24	4	39	3	4%	5%	5%	2%	5%	3%		
Ten or more miss	98	61	72	17	68	7	9%	8%	14%	9%	9%	6%		
Any VF	124	85	86	18	92	8	12%	11%	16%	9%	12%	7%		
Diabetic Neuropat	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 Neur	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 comparision 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

Appears This Way
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1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Lisa Malandro
8/16/04 05:25:12 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Friday, July 09, 2004 10:16 AM
To: 'Parker, Jonathon M (Regulatory Affairs)'
Cc: Malandro, Lisa; Ware, Jacqueline H
Subject: NDA 21-723 Pregabalin Information Request

Jonathan,
Below, please find additional requests from the Division's Medical Officer related to the ongoing review of the above pregabalin application. Please submit your response to these requests in electronic archival format as amendments.

1. Table 12, summary of Protocol 196

A. Explain how the number of patients in each group (e.g. Placebo-low creatinine clearance) was obtained.

Efforts to reproduce the number of patients in each treatment arm that had low or high creatinine clearance (CLcr) using data from the normlab2.xpt data set for this trial have been unsuccessful. The method used was:

Patients that had a baseline CLcr value (n = 368) were sub-setted out
A categorical variable was created in which patients with a CLcr > 60 were considered to have "normal" CLcr, and those with CLcr </= 60 had a "low" one.

Results-Summarizing by ISSPTID, CLcr category ("normal or "low") and treatment group yields different numbers than those in Table 12. Similarly, efforts to reproduce Table 12 using the data from the exposure dataset were unsuccessful.

2. Provide the following information regarding the 2 randomized patients who were not included in the ITT population (i.e. the patients who did not take a single dose of study drug):

a. ISSPTID
b. Treatment arm to which they were assigned
c. Estimated creatinine clearance value
d. Reason for not taking any study drug (i.e. reason for "withdrawal" from the study)

Please contact me if I can be of assistance.
Thanks,
Lisa

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/s/

Lisa Malandro
7/9/04 10:27:58 AM

Malandro, Lisa

From: Malandro, Lisa

Sent: Thursday, July 08, 2004 1:53 PM

To: Malandro, Lisa; 'Parker, Jonathon M (Regulatory Affairs)'

Cc: Ware, Jacqueline H

Subject: RE: NDA 21-723 Pregabalin Information Request

Sorry! here's the real request!

-----Original Message-----
From: Malandro, Lisa
Sent: Thursday, July 08, 2004 1:52 PM
To: 'Parker, Jonathon M (Regulatory Affairs)'
Cc: Ware, Jacqueline H; Malandro, Lisa
Subject: NDA 21-723 Pregabalin Information Request

Jonathan,
Please provide the following information as an amendment to NDA 21-723.

Protocol 1008-196

Provide the assigned treatment group (placebo, 150- 300- or 300/600 mg/d) for the following 105 patients:

- Patients with eligibility exceptions (Section 9.3.1)

- Patients with protocol deviations (Section 9.3.2.1)

- Patients with protocol violations (Section 9.3.2 2)

Thank you,

Lisa

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/s/

Lisa Malandro
7/9/04 04:14:35 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Monday, May 10, 2004 4:58 PM
To: 'Parker, Jonathon M (Regulatory Affairs)'
Subject: NDA 21-723 Pregabalin for PHN Stat Information Request

Request 1.doc (38 KB)

Jonathan,
Attached please find a request for additional information from the Statistical Reviewer for the above referenced application. Please submit responses to these requests in electronic archival format as amendments to NDA 21-446, NDA 21-723, NDA 21-724,

Please contact me if you have any questions.

Thanks,
Lisa

I. General Request for Studies 045, 127, 196 from the Statistical Reviewer:

1. Put an indicator variable for rescue medication in the diardiar data set for studies 045, 127, 196
2. Provide two additional indicator variables under the medsmeds data set for studies 045, 127, 196: One for rescue medication (Yes/No), and the other for prohibited medication (Yes/No).
3. Under the variable "pmedflag", provide explanation of the "concurrent only" label. Does this include any medication taken only after the study is complete or after the subject withdraws from the study? (This question directly refers to ID=14005, 33004, 54001 of study 045).

II. Individual Study Questions:

A. Study 045:

1. Provide explanation on how missing pain scores for patients whose status is "complete" are handled in the analysis. Also, provide explanation on why these were missing. How did you calculate the endpoint mean pain score and how did you classify responder versus non-responder? These patients ID are the following:
    a. ID=46002 (pain scores were available up to day 44)
    b. ID=74009 (pain scores were available up to day 40)
    c. ID=11005 (pain scores were missing from days 40 to 42, days 44 to 47, days 49 to 50, days 52 to 53, and day 55. It is difficult to calculate mean pain score for Week 7 and Week 8 if there are only 2 and 3 data points available in each week, respectively)
2. Provide explanation for patient # 34002 whose status is "adverse event" (i.e. withdrawn) but his/her pain scores were available from day 1 to day 56.
3. Provide a general explanation on how to handle pain scores data two days after last date of DB dose for the following:
    i. ID=34002
    ii. ID=46001
    iii. ID=55004
    iv. ID=60002
    v. ID=63001
    vi. ID=66002
    vii. ID=68008

Data from these patient IDs include pain scores taken more than one day after the last date of DB dose. How did the weekly mean pain score calculated from these individuals? Note that this also affects the responder analysis.
Example 1: ID=34002; status=adverse event; the day after the last date of DB dose is day 42; available pain scores are from Day 1 to Day 56. Are the data from days 43 to 56 not included in calculating weekly mean pain score?
Example 2: ID=68808; status=adverse event; the day after the last date of DB dose is day 3; available pain scores are from Day 1 to Day 7. How did you calculate mean pain score for week 1? Did you impute the score (LOCF or BOCF) or did you calculate the mean score from available data? If it is the latter, which days (of pain scores) did you use?

B. Study 127:

1. From Appendix A.8, there are only 34 protocol violators. What are the identification numbers for the other 2 violators? (Refer to text Section 5.5 p 41 of 2666)
2. Provide explanation on how missing pain scores for patients whose status is "complete" are handled in the analysis. Also, provide explanation on why these were missing. How did you calculate the endpoint (or weekly for ID=4005) mean pain score with missing data and how did you classify responder versus non-responder? These patients ID are the following:
    a. ID=3003 (pain scores were available up to day 49)
    b. ID=3007 (pain scores were available up to day 49)
    c. ID=4005 (pain scores were missing for almost the entire week 4)
    d. ID=4007 (pain scores were available up to day 36)
    e. ID=10004 (pain scores were available up to day 48)
    f. ID=17016 (pain scores were available up to day 49)
    g. ID=17018 (pain scores were available up to day 49)
    h. ID=21001 (pain scores were available up to day 51)
    i. ID=21002 (pain scores were available up to day 50)
    j. ID=21003 (pain scores were available up to day 51)
    k. ID=24002 (pain scores were available up to day 50)
    l. ID=24011 (pain scores were available up to day 52)
    m. ID=28007 (pain scores were available up to day 51)

3. Provide explanation for patient # 31011 whose status is "lack of efficacy" (i.e. withdrawn) but his/her pain scores were only missing from day 42 up to day 49. Pain scores were available after day 49.
4. Provide a general explanation on how to handle pain scores data two days after last date of DB dose for the following:
    i. ID=7004
    ii. ID=14006
    iii. ID=15005
    iv. ID=18014
    v. ID=23002
    vi. ID=26013

    Data from these patient IDs include pain scores taken more than one day after the last date of DB dose. How did the weekly mean pain score calculated from these individuals? (This is the same question as Study 045)

C. Study 196:

1. Provide explanation on how missing pain scores for patients whose status is "complete" are handled in the analysis. Also, provide explanation on why these were missing. How did you calculate the endpoint or weekly mean pain score with missing data and how did you classify responder versus non-responder? These patients ID are the following:
    a. ID=5002 (pain scores were available up to day 77)
    b. ID=7010 (pain scores were missing from day 25 to day 32 and missing from day 61 to 72)
    c. ID=7014 (pain scores were missing from day 2 to day 8 and missing from day 25 onwards)
    d. ID=109012 (pain scores were missing from day 9 to day 29 and missing from day 43 to 64)
2. Provide a general explanation on how to handle pain scores data two days after last date of DB dose for the following:
    i. ID=7004
    ii. ID=11010
    iii. ID=107001
    iv. ID=108002
    v. ID=109011
    vi. ID=109015
    vii. ID=112006
    viii. ID=115002
    ix. ID=119002
    x. ID=123005
    xi. ID=408025
    xii. ID=651002

Data from these patient IDs include pain scores taken more than one day after the last date of DB dose. How did the weekly mean pain score calculated from these individuals? (This is the same question as Study 045, therefore if you could provide a general explanation on how to handle pain scores data two days after last date of DB dose that should be fine)

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/s/

Lisa Malandro
5/10/04 05:05:14 PM

3/5/04

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-723
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: August 30, 2004

Indication requested: Neuropathic pain associated with post-herpetic neuralgia (herpes zoister)

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?		YES	[NO]
If no, did applicant submit a complete environmental assessment?		[YES]	NO
If EA submitted, consulted to Nancy Sager (HFD-357)?		[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 21-446, 21-724 and 21-725.

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:

Discipline	**Reviewer***
Medical:	Mwango Kashoki, MD, MPH
Secondary Medical:	N/A
Statistical:	Joan Buenconsejo, 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?

			N A	YES	NO
CLINICAL MICROBIOLOGY	NA __√__ _	FILE _____		REFUSE TO FILE ___ __	
STATISTICS		FILE __√__ _		REFUSE TO FILE ___ __	
BIOPHARMACEUTICS		FILE _√____		REFUSE TO FILE ___ __	
• Biopharm. inspection needed:				YES	NO
PHARMACOLOGY	NA _____	FILE ___√__		REFUSE TO FILE _____	
• GLP inspection needed:				YES	[NO]
CHEMISTRY		FILE _√____		REFUSE TO FILE ___ ____	
• Establishment(s) ready for inspection?				[YES]	NO
• Microbiology				YES	[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 21-446, 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 Malalndro
Regulatory Project Manager, HFD-170

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

/s/

Lisa Malandro
3/5/04 11:14:16 AM
CSO

NDA 21-723, pregabalin

Additional information pertaining to this section can be found in the action package for NDA 21-446.

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 - [redacted] 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 - [redacted] 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 - [redacted] 08-Dec-1995 - Review

Good, glad to hear that. Please submit the name for re-review 90 days prior to approval.

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 12:12 PM
To: Mahmud, Alina; Beam, Sammie; Culley, Kimberly
Cc: Malandro, Lisa
Subject: RE: DFS Email - [redacted] 08-Dec-1995 - Review

Yes.

-----Original Message-----
From: Mahmud, Alina
Sent: Tuesday, February 03, 2004 12:10 PM
To: Ware, Jacqueline H; Beam, Sammie; Culley, Kimberly
Cc: Malandro, Lisa
Subject: RE: DFS Email - [redacted] 08-Dec-1995 - Review

Hi Jackie,

Will they be keeping the same name for all four indications?

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 11:14 AM
To: Beam, Sammie; Culley, Kimberly; Mahmud, Alina
Cc: Malandro, Lisa
Subject: FW: DFS Email - [redacted] 08-Dec-1995 - Review

Hi Sammie, Kim, and Alina,
Thanks for sending this IND tradename consult response. However, please be aware that the Lyrica (pregabalin) NDA is here & has been here since October 31, 2003. The NDA has been administratively split into 4 NDAs based on indication - one of which has a 6 month priority review clock. The specifics are as follows:
NDA 21-446 is due April 30, 2004 for diabetic peripheral neuropathy.
NDA 21-723 is due August 31, 2004 for post-herpetic neuralgia.
NDA 21-724 is due August 31, 2004 for epilepsy

The NDA was submitted electronically & is located at \\CDSESUB1\N21446\N_000\2003-10-30

Please let me know if I need to send another consult. I didn't send one for the NDA when it arrived based on discussions I had with Sammie in October. Regrets if there was any misunderstanding.

Thanks,
Jackie

-----Original Message-----
From: CDERDocAdmin [mailto:CDERDocAdmin]
Sent: Tuesday, February 03, 2004 7:49 AM
To: WAREJ@cder.fda.gov; TAYLORR@cder.fda.gov; KATZR@cder.fda.gov; HAFFERA@cder.fda.gov; GUINNP@cder.fda.gov; BEAMS@cder.fda.gov; CULLEYK@cder.fda.gov; MAHMUDA@cder.fda.gov
Subject: DFS Email - [redacted] 08-Dec-1995 - Review

Document room close out the following assignments:

		Personnel Code	Sup-Concur	St
[redacted]	08-Dec-1995	Z95	03-Feb-2004	CM

Document Type: Review
Submission Description: Lyrica tradename acceptable
PM activity: PM activity required

Author(s)/Discipline(s)

1. Kimberly Culley, DRUG SAFETY OFFICE REVIEWER

Signer(s)

1. Kimberly Culley
   02-Feb-2004
2. Alina Mahmud
   02-Feb-2004
3. Carol Holquist
   02-Feb-2004
4. Jerry Phillips
   03-Feb-2004

2/2/04

CONSULTATION RESPONSE

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

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:**
October 9, 2003	December 9, 2003	03-0282

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Richardae Taylor, PharmD
Project Manager
HFD-120

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

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. 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.

2. 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.

3. DDMAC finds the proprietary name Lyrica™ acceptable from a promotional perspective.

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

NDA 21-723, pregabalin

Additional information pertaining to this section can be found in the action package for NDA 21-446.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-446
NDA 21-723

Jan. 9, 2004

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 [redacted] 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 Kd, Ki or pKd 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 appended 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

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

/s/

Bob Rappaport
1/9/04 05:23:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA Acknowledgment
Nov. 25, 2003

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.

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

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

/s/

Lisa Malandro
11/25/03 11:51:55 AM

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,

Felicia A. Feldman

cc: L. Castro
E. Harrigan
R. Wittich
R. Clark
M. Phillips (AA)
P. Conwell

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

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).

2. TELEPHONE NUMBER *(Include Area Code)*
(734) 662-5377

3. PRODUCT NAME
Lyrica (pregabalin) Capsules

6. USER FEE I.D. NUMBER
4609

7. 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 COMMERCIALLY
(Self Explanatory)

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

ıblic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing ;tructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. ınd comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

;partment of Health and Human Services
ood and Drug Administration
ER, HFM-99
01 Rockville Pike
ckville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Senior Vice President, Worldwide Regulatory Affairs and Quality Assurance	10/15/2003

RM FDA 3397 (1/03)

NDA 21-446 Item 18

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Response to Sponsor questions
Sep 6 2001

IND
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

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 emaildated 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 [redacted]

Please provide patient profiles for clinical studies [redacted]

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.

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

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

/s/

Cynthia McCormick
9/6/01 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

CAC mtg. mins
Dec. 29, 2000

(see pharm tox section)

ND 49,393
IND 54,280
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,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure