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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-723

Trade Name: Lyrica Capsules, 25-, 50-, 75-, 100-150-, 200-, 225, and 300 mg

Generic Name(s): (pregabalin)

Sponsor: Pfizer Global Research and Development

Agent:

Approval Date: December 30, 2004

Indication: Provides for the management of postherpetic neuralgia

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-723

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Statistical Review(s)	X
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-723

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-723

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

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

Dear Mr. Parker:

Please refer to your new drug application (NDA) dated October 30, 2003, received October 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 25/50/75/100/150/200/225/300 mg.

We acknowledge receipt of your submissions dated November 20, 2003, and January 8, 12, 16, and 30, February 5, 12, 13, 16, 17, 20, 23, 25(3), 26, and 27, March 3, 17, 19, 30, and 31, April 6, 8, 9, 12, 19, 20, 21, 22, and 28, May 3, 4, 13, 17, 18, 19, 25, 26, and 27, June 2, 3, 4, 7, 9, 14, 18, 21, 22, 24, 25, 28, and 29, July 1, 2, 6, 7, 9, 14, 16, 20, 22, 26, and 27, and August 3, 5, 12, 18, 19, 20, 23, 24, and 25, September 3, 7, 8, and 13, October 26, November 1(2) and December 30(2), 2004.

The November 1, 2004, submission constituted a complete response to our August 31, 2004, action letter.

This new drug application provides for the use of LYRICA™ (pregabalin) Capsules for the management of postherpetic neuralgia.

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

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert and for the patient package insert submitted December 30, 2004). Immediate container and carton labels must be identical to those submitted July 9, 2004, with the addition of the word "Capsules" to the established name as agreed upon in the November 3, 2004, teleconference. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDA 21-723.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We note your commitment of December 30, 2004, not to market this drug until the scheduling is finalized. We further note that, when finalized, appropriate revisions should be made to the package insert, the patient-package insert and the product labeling through supplementation of your NDA. This would include the statements detailing the scheduling of Lyrica in the labeling, as required under 21 CFR 201.57 (h)(1).

We remind you of your postmarketing study commitments in your submission to NDA 21-446 dated December 30 2004.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anesthetic, Critical Care and Addiction Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field a21-446 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures

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

/s/

Robert Meyer
12/30/04 04:36:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-723

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-723

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

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

Dear Mr. Parker:

Please refer to your new drug application (NDA) dated October 30, 2003, received October 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 25/50/75/100/150/200/225/300 mg.

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We also acknowledge receipt of your submissions dated August 23 and 25, 2004. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies.

The following CMC deficiencies are based on the review of your amendment dated August 25, 2004.

1. Provide further, adequate justification for the lack of monitoring of [ ] along with its precursor in the drug substance. As you are aware, [ ] is a structural alert compound. In your recent amendment, you provided a clarification to the comparability protocol for the change in the route of drug substance synthesis stating that [ ] the precursor of [ ] would be limited to NMT — PPM, but there is no apparent monitoring or limits placed for [ ] itself.

2. Provide information on the container closure systems used to generate the additional stability data on three batches from Ringaskiddy and four batches from Little Island sites you provided in support of a retest interval of — months for the drug substance.

3. Either revise your proposed shelf life of the 150-, 200-, 225-, and 300-mg capsules to conform to the data provided in the NDA which we believe supports [ ] or provide further data and justification to better support your proposed — shelf-life.

In addition, it will be necessary for you to submit the draft labeling revised as follows:

A. PACKAGE INSERT

1. Based on the most recent recommendations from our Controlled Substances Staff (CSS), the attached label identifies Lyrica as a Schedule IV controlled substance. We understand that the CSS is currently reviewing newly submitted data bearing on this recommendation. The Drug Enforcement Administration (DEA) has the final authority under the Controlled Substances Act (CSA) to determine whether a drug should be controlled and if so, under what schedule. Once this final determination is made, the label may have to be revised to reflect the final schedule as determined by DEA.

2. Revise the WARNINGS and PRECAUTIONS sections to include the recommended language, as enclosed.

3. Address other revisions, as provided by the agency in the enclosed draft label.

C. PATIENT PACKAGE INSERT

1. Revise to reflect the abuse potential and scheduling.

2. Address other agency revisions as proposed in the enclosed draft.

D. CARTON AND CONTAINER LABELS

1. Revise the name to "LYRICA (pregabalin) Capsules."
2. For the 60-count, 100-mg strength container, reduce the font size of the capsule count (60 Capsules) to make it less prominent than the statement of strength (100 mg).
3. Ensure that child-resistant closures are used for bottles intended to be a "unit of dose" (e.g., 60-capsule size) in accordance with the Poison Prevention Packaging Act.

In addition, you must submit the content of labeling in PDF file format as described at 21 CFR 314.50(l)(5). This new submission requirement was published in the *Federal Register* on December 11, 2003 (68 FR 69009) and was effective June 8, 2004. For additional

information, consult the Guidance for Industry: *Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

Additionally, the following deficiencies have been noted. These deficiencies are not approval issues, but we request that you address them as postmarketing commitments if the studies are not completed prior to approval.

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 the propensity of pregabalin to induce CYP-enzyme metabolism.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the review division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

[See appended electronic signature page]

Robert J. Meyer, M.D
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

2 Enclosures:
Revised draft package insert
Revised draft patient package insert

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

/s/

Robert Meyer
8/31/04 02:44:46 PM

49 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling