

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021446Orig1s028

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**Regulatory Project Manager and Clinical Reviewer
LABELING REVIEW
OF THE PRESCRIBING INFORMATION**

Application: sNDA 021446 (b) (4) – Labeling to be combined with the S-028 label for the action on sNDA 21446 S-028. Once S-028 is approved, (b) (4)

Name of Drug: Lyrica Capsules

Applicant: PF PRISM CV, a Division of Pfizer, Inc.

Labeling Reviewed

Submission Date: May 25, 2010 and amended July 15, 2010

Receipt Date: May 25, 2010 and amended July 15, 2010

Background and Summary Description and Review:

1. Purpose

This supplement seeks to add language from postmarketing reports and the revised Investigator Brochure to the following sections of the Lyrica label:

WARNINGS AND PRECAUTIONS (5.8)

ADVERSE REACTIONS, Clinical Trials Experience (6.1)

ADVERSE REACTIONS, Postmarketing Experience (6.2)

DRUG ABUSE AND DEPENDENCE (9.3)

PATIENT COUNSELING INFORMATION (17.7)

Medication Guide

2. Consults and Reviews

Controlled Substances Staff (CSS) consult (April 01, 2011):

- a. CSS was asked to evaluate proposed language in Section 9.3 (Dependence) and to

determine if the language is adequate.

- b. CSS agreed that there needs to be labeling, but said that insufficient information was submitted to evaluate the full range of spontaneously-reported adverse events that occurred following discontinuation of pregabalin. CSS recommended an Information Request to the Sponsor (see below).
- c. CSS recommended the Sponsor conduct a postmarketing study that prospectively and systematically collects adverse event data to determine the profile of withdrawal symptoms that occur during drug discontinuation following long-term pregabalin administration. With concurrence from CSS, it was decided not to send this recommendation to the Sponsor at this time.
- d. CSS requested that DAAAP consult with the Office of Surveillance and Epidemiology (OSE) regarding postmarketing data on discontinuation behavior.

Office of Surveillance and Epidemiology Consult (May 27, 2011):

- a. Based on the recommendations from CSS, OSE was consulted to evaluate the available postmarketing data and provide crude counts of behaviors occurring following discontinuation of pregabalin.
- b. OSE provided an Adverse Event Reporting System (AERS) search, with crude counts and narratives, and came up with 271 reports associated with Lyrica and withdrawal syndrome.
- c. The Division reviewed these data.

3. Information Requests to the Sponsor

- a. The Sponsor was sent an information request based on the recommendations from CSS and modified by DAAAP on April 7, 2011.
- b. The Sponsor responded to the information request on October 11, 2011. This information request response contained data and rationale that were reviewed by the Division. In addition, the response contained a labeling revision in response to Question #1 from the Division:

QUESTION #1:

Provide wording for Section 9.3 that distinguishes between those adverse events observed during a clinical study and those observed during postmarketing surveillance.

RESPONSE:

Original proposed labeling:

9.3 Dependence

~~In clinical studies~~, Following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, (b) (4) or diarrhea [see Warnings and Precautions (5.8)], (b) (4) physical dependence.

Revised Proposed labeling:

In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, or diarrhea [see Warnings and Precautions (5.8)], (b) (4) physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

- c. The Division accepted the Sponsor's revised labeling, with the exception of the following wording in section 9.3 Dependence, and sent an email to the Sponsor on June 14, 2012, requesting concurrence or discussion. The Division also informed the Sponsor that the labeling (b) (4) would be incorporated into the label associated with S-028.

In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, or diarrhea [see Warnings and Precautions (5.8)], (b) (4) consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

- d. On June 18, 2012, the Sponsor sent an email concurring with the Division's revised labeling in section 9.3 Dependence, which deletes (b) (4) and adds "consistent with" in its place.

4. Labeling Reviewed

The labeling language for (b) (4) was added to the revised label for sNDA 21446 S-028. Additions to the labeling are underlined. Deletions are shown using ~~striketrough~~.

HIGHLIGHTS OF PRESCRIBING INFORMATION

RECENT MAJOR CHANGES

Warnings and Precautions (5.8) 6/2012

FULL PRESCRIBING INFORMATION

5.8 Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. Taper LYRICA gradually over a minimum of 1 week rather than discontinuing the drug abruptly.

6.1 Clinical Trials Experience

Other Adverse Reactions Observed During the Clinical Studies of LYRICA

Nervous System – *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, Stupor, Twitching; *Infrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyrimalid syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus

6.2 Post-marketing Experience

The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders – Headache

Gastrointestinal Disorders – Nausea, Diarrhea

Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

In addition, there are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when LYRICA was coadministered with medications that have the potential to produce constipation, such as opioid analgesics. There are also postmarketing reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications.

9.3 Dependence

In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [*see Warnings and Precautions (5.8)*], ^{(b) (4)}-consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

17.7 Abrupt or Rapid Discontinuation

Advise patients to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea. [see *Warnings and Precautions* (5.8)].

MEDICATION GUIDE

How should I take LYRICA?

- Do not stop taking LYRICA without talking to your healthcare provider. If you stop taking LYRICA suddenly you may have headaches, nausea, diarrhea, ^(b)₍₄₎ trouble sleeping, increased sweating, or you may feel anxious. If you have epilepsy and you stop taking LYRICA suddenly, you may have seizures more often. Talk with your healthcare provider about how to stop LYRICA slowly.

A track-changes version of the label is attached to this review.

Recommendations

With the single exception noted above, I recommend that the proposed revisions to the Lyrica label ^(b)₍₄₎ be included in labeling and approved with sNDA 21446 S-028.

Diana Walker, PhD	June 18, 2012
Regulatory Project Manager	Date
Parinda Jani	June 18, 2012
Chief, Project Management Staff	Date
Robert Levin, MD	June 18, 2012
Medical Officer	Date
Frank Pucino, PharmD, MPH	June 18, 2012
Clinical Team Leader	Date
Sharon Hertz, MD	June 18, 2012
Deputy Director	Date

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/s/

DIANA L WALKER
06/18/2012

PARINDA JANI
06/18/2012

ROBERT A LEVIN
06/19/2012

FRANK PUCINO
06/19/2012

SHARON H HERTZ
06/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: May 25, 2012

To: Bob Rappaport, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products
(DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted Medication Guide (MG)

Drug Name (established name): LYRICA (pregabalin)

Dosage Form and Route: Capsules, CV

Application Type/Number: NDA 21-446

Supplement Number: S-028

Applicant: Pfizer, Inc.

1 INTRODUCTION

On December 19, 2011, Pfizer, Inc. submitted for the Agency's review a Prior Approval Efficacy Supplement to their approved New Drug Application, (NDA) 21-446/S-028 for LYRICA (pregabalin) Capsules, CV. The purpose of this Supplement is to seek Agency approval to add a new indication for the management of neuropathic pain associated with spinal cord injury to the Prescribing Information and Medication Guide. The LYRICA (pregabalin) Capsules, CV was originally approved on December 30, 2004 for the management of neuropathic pain associated with diabetic peripheral neuropathy.

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for LYRICA (pregabalin) Capsules and Oral Solution, CV.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed Medication Guide (MG) for LYRICA (pregabalin) Capsules and Oral Solution, CV

2 MATERIAL REVIEWED

- Draft LYRICA (pregabalin) Capsules and Oral Solution, CV Medication Guide (MG) received on December 19, 2011, revised by the Review Division throughout the review cycle, and received by DMPP May 15, 2012.
- Draft LYRICA (pregabalin) Capsules and Oral Solution, CV Prescribing Information (PI) received on December 19, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on May 15, 2012.

3 CONCLUSIONS

- The MG is acceptable as received by DMPP on May 15, 2012.
- During our review of the draft Prescribing Information we note that Table 7, under 6.1 for Controlled Studies in Neuropathic Pain associated with Spinal Cord Injury, includes Fatigue (11.0%) for PGB treated patients and Placebo (4.%). We defer to DAAAP as to whether fatigue should be listed under the most common side effects section of the MG for LYRICA (pregabalin) and included in the Highlights section for Adverse Reactions ($\geq 5\%$ and twice placebo).

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
05/25/2012

LASHAWN M GRIFFITHS
05/25/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 17, 2012

To: Diana Walker, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Samuel M. Skariah, Regulatory Review Officer, DPDP
L. Sheneé Toombs, Regulatory Review Officer, DCDP

CC: Lisa Hubbard, Group Leader, DPDP
Shefali Doshi, Group Leader, DCDP

Subject: NDA #021446/S-028 Lyrica (pregabalin) Labeling Review

OPDP has reviewed the proposed package insert (PI) and Medication Guide (Med Guide) for Lyrica (pregabalin) originally consulted from DAAAP to OPDP on March 6, 2012. OPDP has reviewed the proposed version of these documents forwarded in an email on May 2, 2012. Comments regarding the PI and Med Guide are provided in the marked versions below.

While this supplement provides efficacy and safety data for a proposed neuropathic pain associated with spinal cord injury indication, OPDP has reviewed the entire label and thus may be commenting on sections of the label that are already approved.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the Med Guide, please contact Sheneé Toombs at 301.796.4174 or LaToya.Toombs@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
05/17/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 16, 2012

TO: Diana L. Walker, Regulatory Project Manager
Joshua M. Lloyd, Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan K. Cummins, M.D., M.P.H.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 21446/S-028

APPLICANT: Pfizer, Inc.

DRUG: Pregabalin (Lyrica®)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Management of neuropathic pain associated with spinal cord injury.

CONSULTATION REQUEST DATE: 1/27/2012
CLINICAL INSPECTION SUMMARY GOAL DATE: 5/7/2012
DIVISION ACTION GOAL DATE: 6/20/2012
PDUFA DATE: 6/20/2012

I. BACKGROUND:

Pfizer, Inc., seeks approval to market pregabalin for the treatment of neuropathic pain associated with spinal cord injury (NP-SCI). Pregabalin has analgesic, anxiolytic, and anticonvulsant activity. However, the mechanism of action of pregabalin has not been fully elucidated. Pregabalin has been studied in patients with a variety of pain, neurological, and psychiatric indications, and was first approved by FDA for marketing in capsule form in the United States (US) on December 30, 2004 for treatment of neuropathic pain associated with diabetic peripheral neuropathy and for post-herpetic neuralgia. On June 10, 2005, the FDA approved pregabalin as an add-on therapy for epilepsy. Subsequently, on June 21 2007, the FDA approved pregabalin for the management of fibromyalgia.

This supplemental application is supported primarily by data from two pivotal studies, Study A0081107, entitled, “A 17-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin for the Treatment of Chronic Central Neuropathic Pain After Spinal Cord Injury”, and Study 1008-000-125, entitled, “A 12-week randomized, double-blind, placebo-controlled, parallel-group multicenter study of pregabalin for treatment of chronic central neuropathic pain after spinal cord injury”, sponsored by Pfizer, Inc. Each of these studies evaluated the efficacy of pregabalin given to subjects with central NP-SCI at doses of 150 to 600 mg/day BID.

Planned enrollment for Study A0081107 was 200 subjects (100 in each treatment group). A total of 280 subjects were screened, of those 220 subjects were assigned to study treatment; 112 subjects in the pregabalin group and 107 subjects in the placebo group were treated. A total of 60 centers (1 center in Chile, 3 centers in China, 1 center in Colombia, 3 centers in the Czech Republic, 1 center in Hong Kong, 6 centers in India, 22 centers in Japan, 3 centers in the Philippines, 2 centers in the Russian Federation, and 18 centers in the United States) enrolled subjects. This study was conducted under IND 53763.

Planned enrollment for Study 1008-000-125 was 132 subjects across 10 clinical centers with approximately 10 to 20 subjects per center. Study centers were located in Australia only. A total of 137 subjects were randomized and received study medication (67 and 70 in the placebo and pregabalin groups, respectively). A total of 8 study centers enrolled subjects. The study was not conducted under IND.

Two clinical sites, for each of the two pivotal studies; A0081107 and 1008-000-125, were inspected. These studies and sites were selected for inspection because they were high enrollers for their respective studies.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #004 Michael J. Cousins, M.D. Royal North Shore Hospital Department of Anesthesia and Pain Management Pacific Highway St. Leonards, NSW 2065 Australia	Protocol: 1008-000-125 Number of Subjects: 33	May 7- 10, 2012	Pending Interim classification: VAI
CI#2: Site #006 Guy M. Bashford, M.D. Port Kembla Hospital (Illawarra) Cowper Street Warrawong, NSW 2502 Australia	Protocol: 1008-000-125 Number of Subjects: 21	April 30 – May 3, 2012	Pending Interim classification: VAI
CI#3: Site #1100 Alina Agafina St. Petersburg State Healthcare Institution City Hospital # 40 Kurortnogo Administrativnogo Rajona Borisova ulitsa, 9, lit. B, Sestroretsk St. Petersburg 197706 Russian Federation	Protocol: A0081107 Number of Subjects: 16	April 2-6, 2012	Pending Interim classification: NAI
CI#4: Site #1072 Michael Joseph Creamer, M.D. Rehabilitation Medical Group, P.A. 100 West Gore Street Suite 203 Orlando, Florida 32806	Protocol: A0081107 Number of Subjects: 13	March 13- 23, 2012	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field and EIR has not been received from the field or complete review of EIR is pending and final classification letter has not issued.

- CI#1:** – Dr. Michael J. Cousins
(Site Number 004)
Royal North Shore Hospital
Department of Anesthesia and Pain Management
Pacific Highway
St. Leonards, NSW 2065
Australia

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. What was inspected:** The site screened 38 subjects, 33 subjects were enrolled. Seventeen subjects have completed the study. The study records of 38 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, concomitant medications and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, IRB/Ethics committee correspondence and monitoring and safety reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data source, the subject-entered Daily Pain Rating Scale diary, for each subject was verified. There was no evidence of under-reporting of AEs. The FDA field investigator issued a Form FDA 483 citing 2 minor inspectional observations.

1. An investigation was not conducted in accordance with the investigational plan. Specifically,
 - a. Subject 4028 did not have a traumatic spinal cord injury as required by the protocol. This subject did not meet protocol-specified entry criteria.

OSI Reviewer's Note: The entry criterion violation was reported in the application under protocol deviations for this study as follows; Subject 4028, randomized to the pregabalin group, did not have traumatic spinal cord injury and was withdrawn from the study. This subject did receive 83 days of therapy but was considered ineligible for the study and was considered as not completing the study. According to the applicant, Subject 4028 was included in the efficacy analyses with the exception of any completer analyses.

- b. Subjects 4001, 4004, 4007, 4011, 4023, 4035 and 4038 did not complete certain protocol-specified study visit procedures on at least one study visit, but not screening or baseline assessments, such as: weight, Q-LES-Q, SWLS, BSI18, VAS, SF-MPQ, and waist and hip girth.
2. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically,
 - a. Subject 4005 case history lacked original information sheet.
 - b. Subject 4024 had no source record or CRF to support questionnaire for screening visit.
 - c. Subject 4019 record was missing source (doctor's notes) for Visit 3.

- d. The study file for 4 subjects did not contain a copy of the subject's dosing records which indicated their exact medication bottles.

These were isolated observations of limited import to determination of the primary efficacy or safety variables, were not of a systemic nature, and should not importantly impact data generated by this site.

- c. **Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Cousins' site, associated with Study 1008-000-125 submitted to the Agency in support of NDA 21446 S-028, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2: – Dr. Guy M. Bashford**
(Site Number 006)
Port Kembla Hospital (Illawarra)
Cowper Street
Warrawong, NSW 2502
Australia

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** The site screened 28 subjects, and 26 subjects were enrolled. Thirteen subjects have completed the study. The study records of all 28 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, concomitant medications and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, IRB committee correspondence, and monitoring and safety reports.
- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data source, the subject-entered Daily Pain Rating Scale diary, for each subject was verified. There was no evidence of under-reporting of AEs. The FDA field investigator issued a Form FDA 483 citing 1 inspectional observation.
 1. An investigation was not conducted in accordance with the investigational plan. Specifically,
 - a. Records for Subject 004 indicate that the subject was diagnosed with "ST-T

changes compatible with ischemia”, a protocol exclusion criterion, on August 5, 2002. Subject 004 was subsequently treated with study medication from August 14, 2002 through November 14, 2002.

- b. Records for Subjects 018 and 020 reveal that they did not have a VAS score of at least 40 mm on the SF-MPQ at both study Visit 1 and Visit 2, as required by the protocol. These subjects were subsequently treated with study medication.
- c. Subject 014 and 015 failed to complete the BSI18 for Visit 8.

These were isolated observations, were not of a systemic nature, and should not importantly impact data generated by this site.

- c. **Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Bashford’s site, associated with Study 1008-000-125 submitted to the Agency in support of NDA 21446 S-028, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: Alina Agafina

(Site Number 1100)

St. Petersburg State Healthcare Institution

City Hospital #40

Kurortnogo Administrativnogo Rajona

Borisova ulitsa, 9, lit. B, Sestroretsk

St. Petersburg 197706

Russian Federation

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** The site screened 18 subjects, 16 subjects were enrolled. Thirteen subjects have completed the study. The study records of all 16 enrolled subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, concomitant medications and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, Ethics committee correspondence, and monitoring and safety reports.
- b. **General observations/commentary:** Generally, the investigator’s execution of the protocol was found to be adequate. The primary efficacy endpoint data, the subject-entered Daily Pain Rating Scale diary, for each subject was verified. There was no evidence of under-reporting of AEs. There were a few minor protocol deviations noted

by the FDA field investigator, none of which should importantly impact data reliability. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Agafina's site, associated with Study A0081107 submitted to the Agency in support of NDA 21446 S-028, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- 4. CI#4:** Dr. Michael J. Creamer
(Site Number 1072)
Rehabilitation Medical Group, P.A.
100 West Gore Street
Suite 203
Orlando, Florida 32806

- a. What was inspected:** The site screened 14 subjects, 1 subject was a screen failure and 13 subjects were randomized and treated with test article. Twelve subjects completed the study. The study records of 14 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, concomitant medications and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, 1572s, IRB committee correspondence and monitoring and safety reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data source, the subject-entered Daily Pain Rating Scale diary, for each subject was verified. There were minor observations that were discussed with the site.
1. There was a single minor pain score discrepancy for Subject 013, the result of a single entry transcription error between the subject's daily diary and the CRF.
 2. There were 3 instances where AEs were either under-reported or mis-reported.
 - a. Subject 011 reported feeling lethargic on Day 21, however the event was not recorded on the CRF.
 - b. Subject 014 had trace peripheral edema at Visit 3, however the event was not recorded on the CRF.
 - c. Subject 001 reported drowsiness which was recorded on the CRF, however, this AE was not listed in the AE data listing submitted in the application.

OSI Reviewer's Note: These observations were discussed with the review division medical officer, Joshua Lloyd, on March 27, 2012. Dr. Lloyd and Dr. Iacono-Connors

generally agreed that these were isolated observations, were not of a systemic nature, and should not significantly impact data generated by this site.

Finally, the FDA field investigator issued a Form FDA 483 citing 1 inspectional observation, 3 subjects were found to be taking concomitant analgesic pain medications during the study but not in accordance with the protocol.

1. Per protocol, Section 5.5., Concomitant Medications and Non-Drug Treatments, subjects were allowed to be on certain concomitant medications, specifically analgesics and general skeletal muscle relaxants as “Permitted Treatments” (Table 3), if on a stable dose regimen; defined as starting at least 30 days prior to Visit 1 and throughout study participation. Permitted Treatments were not to be initiated during the study. Source documents at the site show that narcotic analgesic medications were taken by subjects but not in accordance with the protocol. These concomitant medication usages were properly recorded by the site in source records and subject CRFs, however, the sponsor failed to identify these as protocol violations in the data listings submitted to the application NDA 21446 S-028.
 - a. Subject 1072006 Visit 1 was on 3/13/2009, and Visit 8 was on 8/3/2009. The source records showed this subject taking the following concomitant medications while on study.
 - Oxycodone (30 mg/6 hours): beginning in 2003 to 3/27/2009
 - Lortab (10 mg/6 hours): 3/27/2009 to 4/15/2009
 - Oxycodone (15 mg/6 hours): 4/15/2009 to 5/5/2009
 - Oxycodone (30 mg/4 hours): 5/6/2009 to ongoing
 - b. Subject 1072010 Visit 1 was on 8/27/2009, and Visit 8 was on 1/11/2010. The source records showed this subject taking the following concomitant medications while on study.
 - Percocet (10 mg/325 mg): 9/22/2009 to 9/30/2009
 - Baclofen Pump (240 mcg): 10/2009 to 10/19/2009
 - Baclofen Pump (263.3 mcg): 10/19/2009 to Ongoing
 - c. Subject 1072012 Visit 1 was on 11/18/2009, and Visit 8 was on 4/15/2010. The source records showed this subject taking the following concomitant medications while on study.
 - Endocet (10/325): 9/24/2009 to 11/5/2009
 - Oxycodone (15mg): 11/6/2009 to 1/18/2010
 - Endocet (10/325): 1/18/2010 to Ongoing

OSI Reviewer’s Note: These observations were discussed with the review division medical officer, Joshua Lloyd, on March 27, 2012. OSI reviewer Lauren Iacono-Connors informed Dr. Lloyd that these observations all represent protocol violations for use of Permitted Treatments/Concomitant Medications as listed in Table 3 of the protocol, and that while the site did properly record these concomitant medications in source records and subject CRFs, they failed to identify that these were protocol violations. The review division may wish to consider the impact of these protocol violations on study data for these subjects, in particular the primary efficacy endpoint.

Of concern is the fact that the sponsor, Pfizer, did not identify these as protocol violations in their supplement NDA 21446 S-028. However, the sponsor did list these concomitant medications and their use during the study in the data-listing for “concomitant-medications”.

It is possible that the sponsor may not have identified the inappropriate use of narcotic/non-narcotic analgesics and certain muscle relaxers as violations of the protocol for all sites in this study. This observation may be a systemic practice for reporting concomitant medications for this study, and may have a significant impact on the primary efficacy endpoint of subject-reported daily pain.

In order to determine the magnitude of this type of concomitant medication use practice across the study and the potential impact on efficacy, it was recommended in an email from OSI Reviewer, Lauren Iacono-Connors, dated, March 29, 2012, to the review division Medical Officer, Joshua Lloyd, that DAAAP consider requesting that the sponsor, Pfizer, provide a detailed list of all relevant concomitant medication changes that occurred during the conduct of the study, by subject/date/medication/dose. An information request (IR) was issued to Pfizer, and subsequently additional information was submitted to the application to address concomitant medication use practice across the entire study.

In early May 2012, review division Medical Officer Joshua Lloyd contacted OSI reviewer Lauren Iacono-Connors, and informed Dr. Iacono-Connors that the inappropriate concomitant medication use described for Site 1072 (Dr. Creamer) was found at other sites as well. However, this systemic protocol violation did not importantly impact study outcome for efficacy or safety.

- c. **Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Creamer’s site, associated with Study A0081107 submitted to the Agency in support of NDA 21446 S-028, appear reliable based on available information.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of available inspectional findings for clinical investigators Dr. Cousins, Dr. Bashford, Dr. Agafina, and Dr. Creamer, the study data collected, for Study A0081107 and Study1008-000-125, appear reliable in support of NDA 21446 S-028.

Three clinical sites inspected, Dr. Creamer (Site 1072), Dr. Cousins (Site 004), and Dr. Bashford (Site 006), were each issued a Form FDA 483 citing inspectional observations. The final inspection classification for Dr. Creamer (Site 1072), and the preliminary classifications for Dr. Cousins (Site 004) and Dr. Bashford (Site 006) are Voluntary Action Indicated (VAI). The preliminary classification for the remaining inspection, that of Dr. Agafina (Site 1100), are No Action Indicated (NAI).

Inspectional findings for Dr. Cousins and Dr. Bashford revealed isolated observations that were not of a systemic nature, and should not importantly impact safety or efficacy data generated by these sites.

Inspectional findings at Dr. Creamer's site found 3 subjects to be taking concomitant analgesic pain medications during the study [A0081107] but not in accordance with the protocol. In order to determine the magnitude of this concomitant medication use practice across the study and the potential impact on efficacy, it was recommended in an email from OSI Reviewer, Lauren Iacono-Connors, dated, March 29, 2012, to the review division Medical Officer, Joshua Lloyd, that DAAAP consider requesting that the sponsor, Pfizer, provide a detailed list of all relevant concomitant medication changes that occurred during the conduct of the study, by subject/date/medication/dose. An IR was issued to Pfizer, and subsequently additional information was submitted to the application to address concomitant medication use practice across the entire study [A0081107].

In early May 2012, review division Medical Officer Joshua Lloyd contacted OSI reviewer Lauren Iacono-Connors, and informed Dr. Iacono-Connors that the inappropriate concomitant medication use described for Site 1072 (Dr. Creamer) was found at other sites across Study A0081107 as well. A detailed review by Joshua Lloyd revealed that the impact of these inspectional observations should not adversely impact data reliability or study endpoints.

Although regulatory violations were noted as described above they are unlikely to significantly impact primary safety and efficacy analyses for Study A0081107 and Study1008-000-125. Therefore, the data from these studies, submitted in support of NDA 21446 S-028, may be considered reliable based on available information.

Note: Observations noted above are based in part on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan K. Cummins, M.D., M.P.H.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

LAUREN C IACONO-CONNORS
05/16/2012

JANICE K POHLMAN
05/16/2012

SUSAN K CUMMINS
05/16/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 021446	NDA Supplement #: S- 028
Efficacy Supplement: Type SE- 1, New Indication	
Proprietary Name: Lyrica® (pregabalin) Capsules C-V Established/Proper Name: pregabalin Dosage Form: Capsules Strengths: 25, 50, 75, 100, 150, 200, 225 and 300 mg	
Applicant: C.P. Pharmaceuticals International C.V. Agent for Applicant (if applicable): Pfizer, Inc.	
Date of Application: December 19, 2011 Date of Receipt: December 20, 2011 Date clock started after UN: N/A	
PDUFA Goal Date: June 20, 2012	Action Goal Date (if different): N/A
Filing Date: February 18, 2012	Date of Filing Meeting: January 25, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A	
Proposed indication: neuropathic pain associated with spinal cord injury	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 49393, IND 53763, IND 54280, IND 66902, IND 76815, IND 101161, IND 107333, IND 109083 NDA 21723, NDA 21724, NDA 21725, NDA 22488				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	XX			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		XX		
<i>If yes, explain in comment column.</i>			XX	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			XX	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 773 1486">Drug Name</th> <th data-bbox="773 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td data-bbox="203 1486 495 1522"></td> <td data-bbox="495 1486 773 1522"></td> <td data-bbox="773 1486 1060 1522"></td> <td data-bbox="1060 1486 1349 1522"></td> </tr> <tr> <td data-bbox="203 1522 495 1558"></td> <td data-bbox="495 1522 773 1558"></td> <td data-bbox="773 1522 1060 1558"></td> <td data-bbox="1060 1522 1349 1558"></td> </tr> <tr> <td data-bbox="203 1558 495 1587"></td> <td data-bbox="495 1558 773 1587"></td> <td data-bbox="773 1558 1060 1587"></td> <td data-bbox="1060 1558 1349 1587"></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>	<p>YES</p>	<p>NO XX</p>	<p>NA</p>	<p>Comment</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			XX	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	XX			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		XX		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			XX	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	XX			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	XX			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	XX			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	XX			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?			XX	No inspections required
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	XX			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	XX			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	XX			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	XX			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA 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...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			XX	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			XX	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	XX			PeRC Meeting scheduled for April 11, 2012.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	XX			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			XX	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	XX			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		XX		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		XX		Proprietary name already approved in original NDA.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		XX		REMS is not required.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	XX			
Is the PI submitted in PLR format? ⁴	XX			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	XX			Consulted to Patient Labeling
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			XX	No carton and container labeling included.
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		XX		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		XX		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 30, 2011 <i>If yes, distribute minutes before filing meeting</i>	XX			Preliminary comments only, meeting cancelled by Sponsor after receipt.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		XX		There was "No Agreement" on the SPA(s) submitted by the Sponsor.

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 25, 2012

BLA/NDA/Supp #: NDA 021446/S-028

PROPRIETARY NAME: Lyrica

ESTABLISHED/PROPER NAME: pregabalin

DOSAGE FORM/STRENGTH: Capsules,

APPLICANT: 25, 50, 75, 100, 150, 200, 225 and 300 mg

PROPOSED INDICATION: neuropathic pain associated with spinal cord injury

BACKGROUND: The Sponsor submitted an efficacy supplement to add a new indication, neuropathic pain associated with spinal cord injury, and requested priority review. During the pre-NDA phase, there were no SPA agreements reached, and the statistical analysis of the studies for this indication went through Formal Dispute Resolution in 2007. Pre-NDA meeting questions were addressed as of September 30, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	Y
Cross-Discipline Team Leader (CDTL)	Not yet determined		N/A
Clinical	Reviewer:	Joshua Lloyd	Y
	TL:	Jacqueline Spaulding	Y

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Dionne Price	Y
	Supervisor	Tom Permutt	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Newton Woo	Y
	TL:	Adam Wasserman	Y
Product Quality (CMC)	Reviewer:	Ramesh Raghavachari	N
	TL:	James Vidra	N- update given via telephone prior to the meeting.
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connors	Y
	TL:	Susan Leibenhaut	Y
Other attendees	Frank Pucino, Clinical Team Leader Rigoberto Roca, Deputy Division Director Bob Rappaport, Division Director		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: No new Clinical Pharmacology data, will review the labeling.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>BIostatistics</p> <p>Comments: Statistical analysis methods are still in question, but it will be a review issue and not a filing issue.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: No new Nonclinical data, will review the labeling.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: No new CMC data, CMC will review the Environmental assessment and the labeling.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments: Dr. Vidra informed me that CMC would consult the EA officer.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: To be determined</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Mid-Cycle Meeting: March 19, 2012 PeRC Meeting: April 11, 2012 Wrap-Up Meeting: May 14, 2012 Primary Reviews due in DARRTS: May 27, 2012 Label and PMR comments due to Sponsor: May 30, 2012</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): In 74-day letter.</p>

	<u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Diana Walker

February 2, 2012

Regulatory Project Manager

Date

Parinda Jani

February 2, 2012

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

DIANA L WALKER
02/02/2012

PARINDA JANI
02/02/2012