CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-488

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	(Electronic Stamp)
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement #	22-488
Applicant Name	C.P. Pharmaceuticals International C.V. c/o Pfizer Inc.,
Date of Submission	March 4, 2009
PDUFA Goal Date	January 4, 2010
Proprietary Name / Established (USAN) Name	Lyrica®/ pregabalin
Dosage Forms / Strength	Oral solution, 20 mg/mL
Proposed Indication(s)	Neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia. (The intent of this application is not to change the current indication, but to obtain approval of the new formulation)
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Rob Shibuya, M.D.
Pharmacology/Toxicology Review	Kathleen Young, Ph.D. / Adam Wasserman, Ph.D.
CMC Review	Houda Mahayni, Ph.D. / Patrick Marroum, Ph.D. John C. Hill, Ph.D. / Ali Al Hakim, Ph.D. Danae Christodoulou, Ph.D. (CDTL)
Clinical Pharmacology Review	Suresh B. Naraharisetti, Ph.D. / Suresh Doddapaneni, Ph.D.
DDMAC	Twyla Thompson / Mathilda Fienkeng
OSE/DMEPA	LaToya Shenee Toombs, Pharm.D. / Carlos M. Mena-Grillasca, R.Ph. / Denise Toyer, Pharm.D. / Carol Holquist, R.Ph.
OSE/DRISK	Robin Duer, M.B.A., B.S.N., R.N. / Mary Willy, Ph.D.

CDTL = Cross-Discipline Team Leader
CMC = Chemistry, Manufacturing, and Controls
DDMAC = Division of Drug Marketing, Advertising and Communication
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

NDA 21-446 for Lyrica® (pregabalin) Capsules (solid oral dosage form) was approved in December, 2004, for the management of Neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia.

NDA 21-724 was approved in June 2005, for the indication as an Adjunctive therapy for adult patients with partial onset seizures. Subsequently, an efficacy supplement for the indication of management of Fibromyalgia was approved in June 2007.

(b) (4)

The Applicant has submitted an application for a new formulation, an oral solution (20 mg/mL), intended for patients who are unable to swallow the capsules. The formulation is intended to be used for the currently approved indications, and the Applicant is not seeking to amend any of the indications.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling modifications requested by the Applicant.

2. Background

Pregabalin is an alpha$_2$ delta ligand with analgesic, anxiolytic, and anticonvulsant properties. The actual mechanism of action is unknown; however, nonclinical studies suggest that binding to the alpha$_2$ delta auxiliary subunit of voltage-gated calcium channels in central nervous system tissues may be involved in its anti-nociceptive and anti-seizure effects. In vitro studies indicate that pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

Additional studies indicate that, while pregabalin is a structural derivative of the inhibitory neurotransmitter gamma aminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors; it does not augment GABAA responses in cultured neurons; nor does alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, prolonged application of pregabalin to cultured neurons increases the density of GABA transporter protein and increases the rate of functional GABA transport.

Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

The usual starting dose of pregabalin is 150 mg per day, but the final daily dosage regimen depends on the indication:

1. *Diabetic Peripheral Neuropathy*: administered in 3 divided doses per day; may be increased to a maximum of 300 mg/day within 1week.
2. *Post Herpetic Neuralgia*: administered in 2 or 3 divided doses per day; may be increased to 300 mg/day within 1 week, to a maximum dose of 600 mg/day.
3. *Adjunctive Therapy for Adult Patients with Partial Onset Seizures*: administered in 2 or 3 divided doses per day; maximum dose of 600 mg/day.
4. *Fibromyalgia*: administered in 2 divided doses per day; may be increased to 300 mg/day within 1 week, to a maximum dose of 450 mg/day.

As noted in Dr. Christodoulou's review, this application was submitted as a 505(b)(1) application, with cross-reference to the Applicant's original NDA (21-446) for the capsule formulation. Subsequently, no new information was submitted with respect to the non-clinical pharmacology/toxicology, safety or efficacy, or chemistry, manufacturing or controls (CMC) information on the drug substance. Information on the clinical pharmacology and pharmacokinetics was not submitted, based on the premise that pregabalin was determined to be a Biopharmaceutical Classification System (BCS) Class 1 compound with high solubility and permeability characteristics.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The drug product, Lyrica® oral solution (20 mg/mL) is a clear, colorless, flavored solution contained in a 500-mL (16-fluid ounce) white high-density polyethylene bottle with a polyethylene-lined, child-resistant closure. The artificial strawberry flavor (#11545) is not a novel excipient, and is supported by DMF (b) (4), for which the Applicant supplied a Letter of Authorization; the DMF was reviewed and the status was deemed to be adequate. A sweetening agent (sucralose) was also added to the formulation.

A phosphate buffer is used to buffer the solution to a pH of approximately 6.1. The formulation contains methylparaben and propylparaben as part of a preservative system which permits microbiological stability of the formulation throughout its shelf life and intended use life. Accelerated stability studies demonstrated the compatibility of the formulation excipients with the pregabalin drug substance.

One specified process impurity and degradant, (b) (4), is observed and controlled below ICH Q3B qualification threshold. A new degradant, specific to the oral solution, is formed by (b) (4) (b) (4) This new degradant, (b) (4), is observed below ICH Q3B identification and qualification thresholds, and it is controlled as "unspecified" degradant.

The review team determined that the container/closure components are compliant with regulations of indirect food additives; these regulations are relevant since the formulation is an aqueous oral solution and there is low risk of leachables. They also noted that primary stability batches have been manufactured at full production scale using the proposed commercial

process, which has appropriate in-process controls in place and yields a homogeneous solution.

The stability data submitted in the NDA support storage of the drug product for 24 months at, or below, the ICH alternative storage conditions of 30°C ± 2°C (at 35% relative humidity, ± 5%) and a 45-day use period for opened bottles when stored at, or below, 30°C ± 2°C (at 35% relative humidity, ± 5%).

As noted by Drs. Hill and Christodoulou, the data supporting approval of the drug substance, pregabalin, were reviewed at the time of the action on NDA 21-446. The physical characteristics of the drug substance are as follows: crystalline and existing in a single morphic form, it is non-hygroscopic, nonsolvated, thermally stable, and soluble in water. The saturation solubility of pregabalin in aqueous media at room temperature is >30 mg/mL in the pH range 1 to 13. The compound is classified as highly soluble and highly permeable under the Biopharmaceutical Classification System (BCS 1). Since the new formulation is a solution dosage form, it meets the rapidly dissolving criteria, and the applicant's biowaiver request was assessed and granted by ONDQA (Reviewer Dr. Houda Mahayni, August 4, 2009).

In addition, Phase 4 commitments from NDA 21-446 for the drug substance, i.e., testing levels of residual (b) (4) post-approval and implementation of alternate manufacturing protocols, have been fulfilled by the applicant.

Facilities Review/Inspections
The Office of Compliance issued an "Acceptable" cGMP recommendation on April 6, 2009 for all manufacturing facilities.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance, and with the determination that sufficient stability data have been provided to support an expiry period of 24 months at or below the ICH alternative storage. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Applicant referenced NDA 21-446 as support for pregabalin's pharmacology and toxicology. No new non-clinical data were requested, or submitted in support of this application. As noted in Dr. Young's review, since the proposed indication was the same as for the approved product, there were no changes in the proposed maximum recommended daily drug product dose, treatment duration, or patient population. There were no novel excipients in the proposed oral solution formulation, and the impurities and degradation products in the to-be-marketed formulation have been identified and measured below threshold level for qualification.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Pregabalin has been determined to be a Biopharmaceutical Classification System (BCS) Class 1 compound, with high solubility and high permeability characteristics. No clinical pharmacology information was submitted in this NDA. Neither the Applicant nor the clinical pharmacology review team is proposing any changes in the clinical pharmacology section of the label.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Pregabalin is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

There were no additional data required or submitted to support the efficacy of the new formulation. The Applicant referenced their NDA for the capsule formulation (NDA 21-446).

8. Safety

In addition to referencing their NDA for the capsule formulation, the Applicant submitted a safety update comprised of safety data from clinical trials using the capsule formulation. The reported adverse event profile was consistent with the previously identified safety profile during the drug development program; no new safety signals were identified. In addition, the Annual Report for NDA 21-446 (submitted December 11, 2008) was reviewed by Dr. Shibuya; he did not identify any new safety signals.

Manufacturers of oral solution formulations need to address whether it is necessary to provide for a special measuring device to be dispensed with the drug product. Since this product does not have a narrow therapeutic index, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that no special measuring device is necessary.

In December 2008, FDA notified sponsors of all antiepileptic drugs that the risks of suicidal thoughts and behaviors associated with this class of drugs would have to be addressed. A Medication Guide-only REMS was approved in April 2009 for Lyrica® capsules under NDA 21-446. Since the oral solution formulation contains the same drug substance as the capsules, an identical Medication Guide-only REMS would be required for the new formulation.

The Applicant's proposal to revise the Medication Guide and labeling for the capsules in order to be "in common" with the oral solution (NDA 22-488) means that they will have essentially "modified" the original REMS (Medication Guide) for the capsules. Procedurally, the Applicant needed to submit a REMS/Labeling supplement to NDA 21-446 containing the modified REMS document, REMS assessment, and Medication Guide. Simultaneous with the

submission to NDA 21-446, the Applicant also needed to submit the identical REMS to NDA 22-488 as a Proposed REMS. The revised REMS for NDA 21-446 and REMS for NDA 22-488 would then need to be approved simultaneously.

9. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary.

10. Pediatrics

The Applicant had previously submitted pediatric plan with the capsule formulation to meet the requirement to conduct studies in pediatric patients as specified by the Pediatric Research Equity Act (PREA) of 2003. Specifically, as summarized in Dr. Shibuya's review, certain studies are deferred and certain studies are waived:

Waived studies

- The diabetic peripheral neuropathy and post-herpetic neuralgia indications were waived for all age groups because pediatric studies are not practical because there are too few patients to study.
- A partial waiver for the epilepsy indication was granted for pediatric patients age birth to 1 month of age because the condition was not felt to exist in this age stratum.
- A partial waiver for the fibromyalgia indication was granted for pediatric patients age 0 to 12 years-old because pediatric studies are not practical because there are too few patients with the disease to study.

Deferred studies

- A deferral was granted for the epilepsy indication for patients age 2 months to 16 years of age. The final study report is due on April 2015.
- A deferral was granted for the fibromyalgia indication for patients age 13 to 16 years of age. The final study reports are due on January 13, 2012.

An identical pediatric plan was submitted for the oral solution formulation.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Division of Drug Marketing, Advertising, and Communication (DDMAC), the Division of Medication Error Prevention, and Analysis (DMEPA), and the Division of Risk Management (DRISK). Their recommendations were reviewed and incorporated in the appropriate places in the label.

Financial Disclosure

There were no new clinical trials conducted in support of this application. The Applicant submitted forms FDA 3454 and FDA 3455 indicating that the need to certify that there was no financial arrangement with study investigators was not applicable.

There are no other unresolved relevant regulatory issues.

12. Labeling

The Applicant has submitted enough information to support their proposed labeling. As noted above, representatives from the Office of Surveillance and Epidemiology were consulted and their recommendations were incorporated during the discussion of the label.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

I concur with the review team that the Applicant has provided adequate chemistry, manufacturing, and controls data to support quality and performance of the Lyrica® 20 mg/mL oral solution formulation, throughout its proposed shelf-life of 24 months. No new safety findings were identified, and this new formulation does provide a benefit for patients who are unable to swallow capsules; therefore, my overall risk:benefit assessment is in favor of approval of this application.

Recommendation for Post-marketing Risk Management Activities

The REMS approved for this NDA is identical to the REMS approved for the capsule formulation (NDA 21-446).

Recommendation for other Post-marketing Study Commitments

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22488	ORIG-1	PFIZER CHEMICAL CORP	LYRICA (PREGABALIN)

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

/s/

RIGOBERTO A ROCA
01/04/2010