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APPLICATION NUMBER:

22-488

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 20, 2009
From	Danae Christodoulou, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-488
Applicant	Pfizer Inc./C.P. Pharmaceuticals C.V.
Date of Submission	March 4, 2009
PDUFA Goal Date	January 4, 2009
Proprietary Name / Established Name	LYRICA®/ (pregabalin) oral solution
Dosage forms / Strength	Oral solution, 20 mg/ml
Proposed Indication(s)	Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia
Recommended	Approval

1. Introduction

Lyrica® (pregabalin) oral solution 20 mg/ml is a new pregabalin formulation for oral administration. This dosage form is intended for use in approved indications of pregabalin in adult patients, who may require or benefit from an oral solution (e.g., may have difficulty in swallowing capsules). The solution strength is 20 mg/ml for flexible dosing up to 30 ml daily, which is equivalent to 600 mg pregabalin. The solution is to be administered in 2 or 3 divided doses per day, with or without food. Lyrica® (pregabalin) capsules, 25, 50, 75, 100, 150, 200, 225, 300 mg was approved in December 30, 2004 under NDA 21-446, for the following indications: Neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia.

NDA 22-488 is submitted as a 505(b)(1) application, with the non-clinical pharmacology and toxicology, clinical pharmacology, pharmacokinetics and bioavailability, as well as safety and efficacy sections cross-referenced to NDA 21-446 with no new information submitted. All results and conclusions and the current approved label for pregabalin capsules remain valid for the current NDA. In addition, chemistry, manufacturing and controls (CMC) information pertaining to the drug substance, pregabalin, is cross-referenced to NDA 21-446. This application includes a quality section to support the oral solution formulation of pregabalin. The NDA was filed based on biowaiver agreements, i.e., exception of a Biopharmaceutical Classification System (BCS) Class 1 compound from bioequivalence studies. The biowaiver has been granted by ONDQA (Reviewer Dr. Houda Mahayni).

The proprietary name Lyrica® remains the same for this product.

2. Background

The approved pharmaceutical equivalent to Lyrica® oral solution, is Lyrica® capsules. Both are immediate release products for oral administration.

Pregabalin is an alpha-2-delta ($\alpha 2\text{-}\delta$) ligand that has analgesic, anxiolytic, and anticonvulsant activity. It is a substrate for System L amino acid transporters, which mediate transport of large neutral amino acids through the epithelial cells of blood-tissue barriers (BBB and placenta), small intestine, renal proximal tubules. Nonclinical studies (NDA 21-446) indicated that pregabalin crosses blood brain barrier and placenta. This carrier-mediated transport process may be involved in the absorption, distribution and elimination of pregabalin in humans. Elimination of pregabalin is primarily (>90%) via renal excretion of the unchanged drug with a terminal elimination half-life of approximately 6 hours in subjects with normal renal function. Pregabalin undergoes negligible metabolism in humans with the major metabolite a N-methylated derivative.

Pregabalin is a BCS Class 1 drug with a high oral bioavailability ($\geq 90\%$), with peak plasma concentrations occurring within 1.5 hours under fasting conditions. Lyrica® capsules exhibit linear pharmacokinetics with both C_{max} and AUC dose proportional within the therapeutic dose range. Since pregabalin was determined to be a BCS Class 1 compound of high solubility and high permeability (NDA 21-446), and the new formulation is a solution, the biowaiver request is granted (NDA 22-488).

3. CMC/Device

Dr. John Hill reviewed the Chemistry, Manufacturing and Controls (CMC) data of this NDA (reviews dated August 4, 2009 and November 6, 2009).

Lyrica® oral solution, 20 mg/ml is a clear, colorless, and flavored solution contained in a 500-mL (16 fluid ounce) white high-density polyethylene bottle with a polyethylene-lined, child-resistant closure. A sweetening agent (sucralose) and flavor (artificial strawberry) are added to mask the bitter taste of pregabalin. The artificial strawberry flavor #11545 is not a novel excipient, and is supported by DMF (b) (4) (Letter of Authorization provided, status adequate). The solution is buffered to approximately pH 6.1 with phosphate buffer. The formulation includes a preservative system consisting of methylparaben and propylparaben providing adequate 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 ICHQ3B qualification threshold. A new degradant, specific to the oral solution, is formed by (b) (4)

This new degradant, (b) (4), is observed below ICHQ3B identification and qualification thresholds, and it

is controlled as “unspecified” degradant. With respect to container/closure compatibility with the drug product, Dr. Hill noted that the applicant justified that the container/closure components are compliant with regulations of indirect food additives and that these regulations are relevant since the formulation is an aqueous oral solution and there is low risk of leachables. 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 support storage of the drug product for 24 months at or below the ICH alternative storage conditions of 30°C +/- 2°C/35% Relative Humidity (RH) +/- 5% and a 45 day use period for opened bottles when stored at or below 30°C +/- 2°C/35% RH +/- 5%.

Drug Substance (reviewed in NDA 21-446)

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit ($\alpha 2$ - δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. Binding to the $\alpha 2$ - δ site is required for analgesic, anticonvulsant and anxiolytic activity in animal models. Pregabalin is crystalline and exists in a single morphic form. It is non-hygroscopic, non-solvated, thermally stable, and soluble in water. At room temperature, the saturation solubility of Pregabalin in aqueous media 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).

Phase 4 commitments in NDA 21-446 for the drug substance, i.e., testing levels of residual (b) (4) post-approval and implementation of alternate manufacturing protocols, were fulfilled by the applicant. Current specifications for pregabalin drug substance have been included in NDA 22-488.

Overall, Dr. Hill recommended Approval of NDA 22-488 (review dated November 6, 2009) based on satisfactory resolution of CMC deficiencies communicated to the applicant during review and the overall “Acceptable” cGMP recommendation made on April 6, 2009 by the Office of Compliance for all manufacturing facilities.

NDA 22-488 contains adequate and appropriate descriptions of the manufacture, characterization, controls and quality of the Lyrica® oral solution, 20 mg/mL. Sufficient stability data have been provided to support an expiry period of 24 months at or below the ICH alternative storage.

4. Nonclinical Pharmacology/Toxicology

For NDA 22-488, no new Pharmacology/Toxicology data were submitted. In her review memo, Dr. Kathleen Young, reviewing pharmacologist, concluded that the non-clinical pharmacology and toxicology information cross-referenced to NDA 21-446 under the capsule form, fully characterized pregabalin, and that is acceptable to support the liquid formulation in NDA 22-488. In addition, she noted that there are no novel excipients in the new formulation. The drug product consists of pregabalin (20 mg/ml), methylparaben

(methyl parahydroxybenzoate), propylparaben (propyl parahydroxybenzoate), monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545, and purified water vehicle. The excipients are pharmacopeial, except for Artificial Strawberry Flavor # 11545. The Artificial Strawberry Flavor #11545 is found in another, approved drug product and has GRAS status for inclusion as a flavoring agent in foods. Additionally the flavoring is referenced to DMF (b) (4), (Letter of Authorization provided, status adequate). The impurities and degradation products in the proposed drug product have been identified and measured below ICH Q3B threshold level for qualification, and have been acceptable by the Chemistry, Manufacturing and Controls review team.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted with this application. In his review memo, Dr. Suresh Narahariseti, reviewing clinical pharmacologist, noted that pregabalin has been determined to be a Biopharmaceutical Classification System (BCS) Class 1 compound with high solubility/high permeability characteristics and referred to the clinical pharmacology review for NDA 21-446 by Dr. Sue Chih Lee, dated March 22, 2004, for additional details on this classification and other relevant clinical pharmacology information. Dr. Narahariseti noted that since the new formulation is a solution dosage form, it meets the rapidly dissolving criteria, and referred to the applicant's biowaiver request which was assessed and granted by ONDQA.

No clinical pharmacology related labeling changes were proposed by the applicant. Dr. Narahariseti did not propose clinical pharmacology changes either and recommended that the submission is acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable for this product.

7. Clinical/Statistical- Efficacy

No clinical data were initially submitted except for a request for waiver of pediatric studies. No statistical review was conducted for NDA 22-488.

In his review memo, Dr. Robert Shibuya, clinical team leader, noted that there are no new efficacy or safety findings submitted with this application, except for the pediatric plan and the Risk Evaluation and Mitigation Strategies (REMS). In addition, he noted several revisions to be implemented to the proposed common labeling, which are summarized in the appropriate section.

Dr. Shibuya concludes the application to be recommended for approval.

8. Safety

In his review memo, Dr. Robert Shibuya, clinical team leader, noted that there are no new safety findings submitted with this application. However, he described the REMS (MedGuide-only) associated with pregabalin. The following is extracted from Dr. Shibuya's memo:

Risk Evaluation and Mitigation Strategies (REMS)

In December 2008, FDA notified sponsors of all antiepileptic drugs (AED) that the risks of suicidal thoughts and behaviors associated with this class of drugs would have to be addressed. Thus, Lyrica® capsules (NDA 21-446) was required to have a Medication Guide- (MedGuide) only REMS as well as certain labeling changes. The MedGuide-only REMS for Lyrica® capsules was approved in April 2009 under NDA 21-466.

Given that the pregabalin oral solution falls into the AED class, an identical MedGuide-only REMS would be required for the new product. (Note that Dr. Phillip Sheridan of the Division of Neurology Products is the medical reviewer for the epilepsy indication.)

Pfizer has proposed to revise their MedGuide and labeling to be "in common" for both the capsules and the oral solution (NDA 22-488). In doing this, they have essentially "modified" their original REMS (MedGuide) so that both NDAs can "share" a REMS.

Procedurally, at this time, the Applicant must submit a REMS/Labeling supplement to NDA 21-466 containing the modified, in common, REMS document, REMS assessment, and MedGuide. Simultaneous with the submission to NDA 21-466, Pfizer should submit the identical REMS to NDA 22-488 as an amendment coded Proposed REMS.

The revised REMS for NDA 21-446 and REMS for NDA 22-488 would be approved simultaneously.

9. Advisory Committee Meeting

This product was not discussed at an Advisory Committee meeting.

10. Pediatrics

The following assessment on Pediatrics is extracted from Dr. Robert Shibuya's memo:

The pediatric plans for the pregabalin capsule formulation have been reviewed by the Pediatric Research Committee (PeRC) during the review of the initial NDA 21-446 and subsequent supplements. The current, comprehensive Pediatric Plan for the capsule formulation is summarized below:

- Waived studies

- The diabetic peripheral neuropathy and post-herpetic neuralgia indications were waived because pediatric studies are impracticable 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-old 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 0-12 years-old because pediatric studies are impracticable 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-old to 16 years-old.
 - A deferral was granted for the fibromyalgia indication for patients age 13 years-old to 16 years-old.

In the initial NDA submission for this oral solution, Pfizer did not submit a pediatric plan, asserting that all pediatric studies should be waived because of the existing requirement for the capsule formulation. However, as a new formulation, the Pediatric Research Equity Act (PREA) was triggered and the Applicant was asked to submit a pediatric plan. In response to a request from FDA, Pfizer submitted a pediatric plan identical to the current agreements for the capsule formulation.

This plan was reviewed by PeRC and found to be acceptable.

Due dates:

- Fibromyalgia – January 31, 2012 for final study reports (tentative)
- Epilepsy – April 2015 for final study reports

11. Other Relevant Regulatory Issues

Patent

US Patent number 5563175 for this product was issued to the applicant (then Warner-Lambert Co.) in October 8, 1998 and does not expire until October 8, 2013.

Manufacturing Facilities

An overall “Acceptable” cGMP recommendation was made on April 6, 2009 by the Office of Compliance for all manufacturing facilities.

Controlled Substance Scheduling – Schedule V

The applicant proposed that the abuse liability (Schedule V for the capsule formulation) is not different for this oral solution. The Controlled Substances Staff (CSS) noted that, if a relative bioavailability study had shown a shorter Tmax or higher Cmax, further abuse liability studies would be required. Additional pharmacokinetic studies have not been

conducted since this product received a biowaiver. In the absence of additional data, CSS accepted the Schedule V classification.

At this time, the following are pending:

- (1) Agreement on labeling revisions between FDA and the applicant
- (2) Approval of the REMS (MedGuide-only) plan

12. Labeling

The applicant proposed a common label to include Lyrica® oral solution 20mg/ml in the approved label for Lyrica® capsules.

At this time, the review team is making labeling changes and agreement with the applicant on the labeling changes is pending.

Dosing (measuring) device

Because this product does not have a narrow therapeutic index, the Division of Medication Error Prevention and Analysis (DMEPA) recommended that no special measuring device is necessary.

The following labeling recommendations are extracted from Dr. Robert Shibuya's review memo:

1. Appropriate modifications to reflect the new 20 mg/ml dosage form to relevant sections of the package insert and Medication Guide are necessary.
2. DMEPA has recommended two substantial revisions to Section 2.5, dosing in patients with renal impairment.
 - a. The table for dosage adjustment is potentially confusing, particularly with regard to the fact that the Applicant uses the term "TID" or "BID" for dose regimen. While the careful reader will note that the adjusted dose refers to total daily dose and note that the dose is to be divided into two or three doses, Dr. Shibuya agrees with DMEPA that there is a substantial risk that prescribers will simply note the number of milligrams in the appropriate box and write that dose BID or TID without dividing it. DMEPA noted that this medication error has been observed with the capsule formulation.
 - b. The supplemental dose following hemodialysis has a broad range and there is no guidance for the prescriber with regard to which dose to choose. For example, a patient on a 25 mg QD regimen could receive from 25 to 75 mg as a single, supplemental dose. Dr. Shibuya agrees that Pfizer should provide more information to guide the prescriber.
3. Per the Physicians Labeling Requirement principles, the use of "should" will be minimized and changed to active voice.

13. Recommendations/Risk Benefit Assessment

The applicant provided adequate CMC data to support quality and performance of the Lyrica® 20 mg/ml oral solution formulation, throughout its proposed shelf-life of 24 months. The oral solution provides convenience of dosing to patients that may require or benefit from an oral solution, in approved indications for Lyrica® capsules. The NDA may be approved based on the biowaiver request for a BCS 1 drug, granted by ONDQA. There were no new safety or efficacy findings in NDA 22-488. All safety, efficacy, non-clinical toxicology and clinical pharmacology sections cross-referenced to NDA 21-446 for Lyrica capsules, have been acceptable by the relevant reviewing disciplines, to support NDA 22-488. As such, Lyrica® 20 mg/ml oral solution has acceptable benefit to risk profile.

At this time, the following are pending:

- (1) Agreement on labeling revisions between FDA and the applicant;
- (2) Approval of the REMS (MedGuide-only) plan.

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

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/s/

DANAE D CHRISTODOULOU
11/23/2009
Cross-Discipline TL Review

PRASAD PERI
11/23/2009
I concur