

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-488**

**MEDICAL REVIEW(S)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Division of Anesthesia, Analgesia, and Rheumatology Products**  
**Bldg 22, Rm 3105 10903 New Hampshire Ave Silver Spring, MD**  
**Tel: (301) 796-2280**

### **Clinical Team Leader Memo**

**To:** NDA 22-488  
Lyrica (pregabalin oral solution), 20 mg/mL

**From:** Robert B. Shibuya, M.D., Clinical Team Leader  
Division of Anesthesia, Analgesia, and Rheumatology Products

**Submission dates:** 4 March 2009 (Initial NDA submission)  
10 July 2009 (Pediatric Plan)

**Date:** 16 December 2009

---

### **Background**

Lyrica® (pregabalin capsules) was initially approved in December 2004 (NDA 21-446) as a solid oral formulation (capsule). The drug is currently approved for four indications:

1. Neuropathic pain associated with diabetic peripheral neuropathy
2. Post herpetic [sic] neuralgia
3. Adjunctive therapy for adult patients with partial onset seizures
4. Fibromyalgia

Pfizer wishes to market a new formulation of pregabalin, an oral solution. Because pregabalin is a Biopharmaceutical Classification System (BCS) Class 1 compound, a biowaiver was granted and this application consists, almost entirely, of chemistry/manufacturing/controls (CMC) data. No clinical data were initially submitted except for a request for waiver of pediatric studies.

Dr. Danae Christodoulou is the Cross-Discipline Team Leader for this application. This memo is limited to the clinical issues [Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP indications) only] related to the new formulation. Dr. Phillip Sheridan of the Division of Neurology Products is the medical reviewer for the epilepsy indication.

## **Pediatrics**

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

- 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 at PeRC and found to be acceptable.

### Due dates:

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

## **Risk Evaluation and Mitigation Strategies (REMS)**

In December 2008, FDA notified sponsors of all antiepileptic drugs (AEDs) 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 April 2009 under NDA 21-466.

Given that pregabalin oral solution falls into the AED class, an identical MedGuide-only REMS will be required for the new product.

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 (the MedGuide). Both NDAs can "share" a REMS, including the Med Guide.

The Applicant has submitted a REMS/Labeling supplement to NDA 21-466 containing the modified, in-common REMS document, REMS assessment, and MedGuide. Simultaneously, Pfizer submitted the identical REMS to NDA 22-488 as an amendment.

The revised REMS for NDA 21-446 and REMS for NDA 22-488 has cleared the consulting divisions with minimal edits and is acceptable to me.

### **Miscellaneous issues**

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

The Applicant asserted 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 T<sub>max</sub> or higher C<sub>max</sub>, further studies abuse liability studies would be required. However, such pharmacokinetic data are not available since this product received a biowaiver. In the absence of data, CSS believes that the Schedule V classification is appropriate.

### **Labeling recommendations:**

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 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. There is a risk that prescribers will simply note the number of milligrams in the appropriate box and write that dose BID or TID without dividing it.
  - 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. The "≥" sign could be used to limit the potential dose range.
3. Per the Physicians Labeling Requirement principles, the use of "should" will be minimized and changed to active voice.

Due to the complexity of the information to be conveyed in the renal dosing table, an acceptable revision was not able to be negotiated by the PDUFA date. In fact, Pfizer's first attempt at clarifying the table resulted in a table that was felt to be more confusing than the original. Thus, the oral solution will be approved with the "old" table and a revised table will be introduced as a labeling supplement at a later date.

**Recommendation:**

Approval

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/  
-----

ROBERT B SHIBUYA

12/17/2009