APPLICATION NUMBER:

209501Orig1s000

SUMMARY REVIEW
1. Introduction

Pfizer (Applicant) submitted this 505(b)(1) new drug application (NDA) for LYRICA CR (pregabalin ER tablets) for three indications: management of post-herpetic neuralgia (PHN), management of pain of diabetic peripheral neuropathy (DPN), and management of fibromyalgia (FM). LYRICA CR is an extended-release (ER) formulation of pregabalin, an agonist of the alpha2-delta subunit of voltage-gated calcium channels in the central nervous system. Pregabalin was approved as an immediate-release (IR) capsule (Lyrica) in 2004 and is currently approved for DPN, PHN, FM, neuropathic pain associated with spinal injury, and as adjunctive therapy in adults with partial onset seizures. The Orange Book shows no approved generic forms of Lyrica although there is an oral solution formulation approved for the same indications, also owned by Pfizer. The IR capsule and the solution share the same labeling; the oral solution was approved without additional clinical studies. The IR capsule will be referenced as “Lyrica” and the ER tablet as “LYRICA CR” [Applicant’s proposed tradename] throughout the text in this review.

Lyrica is dosed two or three times per day. LYRICA CR is designed to be dosed once a day. Pfizer purports that the benefits of the extended-release properties are enhanced patient compliance and convenience. LYRICA CR was developed under INDs 53763 and 107333 (DAAAP/DAARP) Pfizer conducted one efficacy study of LYRICA CR in patients with epilepsy (Study A0081194)
which failed to show efficacy and the Applicant has not proposed the epilepsy indication in this application.

Thus, this review will focus on the pain indications. The key agreements pertinent to the peripheral neuropathic pain and FM indications made during the development cycle were 1. A relative bioavailability approach, bridging the new formulation to the IR formulation was acceptable, 2. At least one efficacy trial in one neuropathic pain condition (PHN or DPN) and [REDACTED] would be required to support approval of these indications, respectively, for a change in formulation from IR to ER, and 3. Pediatric studies in the pain indications could be waived. [REDACTED]

The data submitted in this NDA are generally unremarkable and are typical for an IR to ER reformulation of a known analgesic moiety. Again, while this is a 505(b)(1) NDA, the Applicant owns all of the data for the pregabalin molecule and the Agency made use of the existing data to streamline development. Specifically, this obviated the requirement for replicated efficacy studies and a substantial proportion of the nonclinical package. One efficacy study for each indication was required to demonstrate that the PK profile provided by this novel, extended-release formulation was suitable to provide efficacy for the intended dosing interval for the proposed indications. This review will focus on 1. The failed FM study (Study A0081245 [Study 1245]) [REDACTED]

2. Safety issues potentially related to the reformulation, 3. A potential emerging concern around abuse and overdose of this DEA Schedule V compound.

2. Background

Pregabalin is an active pharmaceutical ingredient that has been marketed for over 12 years and is in extensive clinical use. While the exact mechanism of action of the drug is not entirely clear, it is an analog of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Pfizer’s goal in developing the ER formulation was to match the AUC of the equivalent daily dose of the IR formulation with a lower $C_{\text{max}}$ and similar $C_{\text{min}}$. The formulation succeeded in the first two goals and failed on the last goal. The properties of the formulation also resulted in a complicated dosing regimen where the ER formulation had to be taken with the evening meal to best approximate the pharmacokinetics of the IR formulation. Among other factors that will be discussed later, these formulation limitations likely contributed to the failure of the fibromyalgia trial. Given that this review focuses on the pain indications, I have not addressed why the epilepsy trial failed in this review.

There are no other scientific, clinical, or regulatory areas that were not covered in Section 1 that warrant further description here.

3. CMC/Device
LYRICA CR are film-coated tablets for the 82.5, 165, and 330 mg tablets, respectively. The tablets are of identical size and shape and are differentiated by film coat colors and imprinting. The manufacturing process supported with adequate stability data.

General product quality considerations

- The application technical lead was Ciby Abraham, PhD.
  - The drug substance review was conducted by Debasis Ghosh, PhD with secondary concurrence by Donna Christner, PhD.
  - The Drug Product review was conducted by Chris Hough, PhD.
  - The process review was conducted by Shujun Chen, PhD with secondary concurrence by Haitao Li, PhD.
  - The Biopharmaceutics review was conducted by Kelly Kitchens, PhD with secondary concurrence by Haritha Mandula, PhD.
- All disciplines either considered the data reviewed acceptable or recommended approval. The biopharmaceutics team has recommended that the Applicant add an additional dissolution time point of 9 hours to their dissolution methodology and specifications and to submit those data for Agency review.

Facilities review/inspection

The Facilities review was conducted by Christina Capacci-Daniel, PhD who reviewed the drug substance, manufacturing, and packaging and labeling facilities. She found the facilities acceptable.

Other notable issues (resolved or outstanding)

There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Kevin Snyder, PhD with secondary concurrence by Newton Woo, PhD and Dan Mellon, PhD. The nonclinical team has recommended approval for LYRICA CR with no labeling changes recommended. The summary of the nonclinical review is reproduced verbatim from Dr. Snyder’s excellent review.

No new toxicology studies were required for LYRICA CR as plasma exposures were within levels associated with labelled use of the immediate-release formulation. The extended-release LYRICA CR formulation contains several excipients that are not present in the original immediate-release formulation. Of these excipients, Kollidon SR was the only one with a maximum daily intake (MDI) that exceeded levels found in other FDA-approved drug products with similar indications at the time of the IND submission. To qualify the safety of this excipient, the Applicant submitted PK/ADME studies in rats and dogs demonstrating limited to no systemic absorption after oral administration as well as a 6-month repeat-dose toxicology study in dogs, which established a NOAEL of 2000 mg/kg/day. Using allometric scaling based on body
surface area, this NOAEL is roughly equivalent to a human equivalent dose of 66,667 mg/day, providing a 60-fold safety margin for Kollidon SR based on the maximum human recommended dose of LYRICA CR. Additionally, the specifications for drug substance impurity (NMT 0.4%, NMT 0.5%) and the drug product (NMT 0.2%, NMT 0.2%) exceed the qualification limits of NMT 0.15% and NMT 0.2% prescribed in ICH Q3A(R2) and ICH Q3B(R2), respectively; however, these specifications were reviewed and deemed acceptable during the review of the original immediate-release LYRICA (pregabalin) approval and are thus acceptable in the current application. There are no outstanding nonclinical safety issues.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Srikanth Nallani, PhD with secondary concurrence from Yun Xu, PhD. The clinical pharmacology team has recommended approval for LYRICA CR.

The overall goal of the clinical pharmacology program was to establish a bridge between LYRICA CR AND Lyrica, specifically to achieve equivalent AUC with a lower C_{max} and similar C_{min} to the comparable Lyrica dose. The pregabalin moiety has been well characterized. It is a BCS Class 1 molecule (high solubility, high permeability) that is primarily absorbed in the small intestine and proximal colon and largely excreted, unchanged, renally. A total of 12 Phase 1 studies were conducted to support this application, summarized in the table following.

Overview of Phase 1 Studies Evaluating LYRICA CR in Healthy Volunteers
<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Objective</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preliminary Multiple Dose Study</strong> Evaluating PK, Relative Bioavailability, and Dose Proportionality</td>
<td>To evaluate the steady-state PK, extent of absorption, safety, and tolerability of 82.5 mg ER1, 165 mg ER1, and 330 mg ER administered QD following a 000-750 kcal medium-fat evening meal as compared to pregabalin 150 mg IR capsule administered fasted q12.</td>
<td>82.5 mg ER1, QD 165 mg ER1, QD 330 mg ER, QD</td>
</tr>
<tr>
<td>A0081225 (20)</td>
<td></td>
<td>150 mg IR, q12</td>
</tr>
<tr>
<td><strong>Multiple Dose Studies</strong> Evaluating PK, Relative Bioavailability, and Dose Proportionality</td>
<td>To evaluate the steady-state PK, extent of absorption, safety, and tolerability of the 330 mg ER tablet and 2x165 mg ER tablets administered QD following a 600-750 kcal medium-fat evening meal as compared to the pregabalin 150 mg IR capsule administered fasted q12. In addition, to evaluate PK and extent of absorption of 2x165 mg ER relative to 1x330 mg ER.</td>
<td>330 mg ER, QD 2x165 mg ER, QD 150 mg IR, q12</td>
</tr>
<tr>
<td>A0081198 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the steady-state PK, extent of absorption, safety, and tolerability of the 82.5 mg ER tablet administered QD following a 600-750 kcal medium-fat evening meal relative to the pregabalin 25 mg IR capsule administered fasted TID.</td>
<td>82.5 mg ER, QD 25 mg IR, TID</td>
</tr>
<tr>
<td>A0081215 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the steady-state PK, extent of absorption, safety, and tolerability of 2 x 330 mg ER tablets administered QD following a 600-750 kcal medium-fat evening meal relative to the pregabalin 300 mg IR capsule administered fasted q12.</td>
<td>2 x 330 mg ER, QD 300 mg IR, q12</td>
</tr>
<tr>
<td>A0081216 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the PK, extent of absorption, safety, and tolerability of the 165 mg ER tablet and 2 x 82.5 mg ER tablets administered QD following a 000-750 kcal medium-fat evening meal as compared to the pregabalin 75 mg IR capsule administered fasted q12. In addition, to evaluate PK and BA of the 330 mg ER tablet administered fed relative to the 330 mg ER tablet administered fasted.</td>
<td>165 mg ER, QD 2 x 82.5 mg ER, QD 75 mg IR, q12</td>
</tr>
<tr>
<td>A0081226 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-Dose Studies** Evaluating Impact of Time of Day and Food on PK and Relative Bioavailability**</td>
<td>To evaluate the PK and extent of absorption of the 330 mg ER tablet administered following an 800-1000 kcal low-, medium- or high-fat evening meal relative to the pregabalin 300 mg IR capsule administered following an 800-1000 kcal medium-fat evening meal.</td>
<td>330 mg ER 300 mg IR</td>
</tr>
<tr>
<td>Evening Administration</td>
<td>A0081227 (28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the PK and extent of absorption of the 330 mg ER tablet administered following an 800-1000 kcal low-, medium- or high-fat evening meal relative to the pregabalin 300 mg IR capsule administered following an 800-1000 kcal medium-fat evening meal.</td>
<td>330 mg ER 300 mg IR</td>
</tr>
<tr>
<td>A0081228 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning Administration</td>
<td>A0081239 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the PK and extent of absorption of the 330 mg ER tablet administered following a 400-500, 600-750 and 800-1000 kcal medium-fat breakfast relative to the pregabalin 300 mg IR capsule administered fasted in the morning.</td>
<td>330 mg ER 300 mg IR</td>
</tr>
<tr>
<td>Mid-Afternoon Administration</td>
<td>A0081188 (28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To evaluate the PK and extent of absorption of the 330 mg ER tablet administered following a 400-500, 600-750, and 800-1000 kcal medium-fat lunch relative to the pregabalin 300 mg IR capsule administered fasted in mid-afternoon.</td>
<td>330 mg ER 300 mg IR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Drug Interaction Study—Single Dose Pregabalin ER and Multiple Dose Prokinetic Drug

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Description</th>
<th>Dose/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0081197</td>
<td>To evaluate the effect of the gastrointestinal prokinetic medication erythromycin on the PK and extent of absorption of pregabalin ER administered following a 600-750 kcal, medium-fat evening meal.</td>
<td>330 mg ER Erythromycin 500 mg q6 for 3 doses.</td>
</tr>
<tr>
<td>A0081309</td>
<td>To provide clinical PK data to evaluate the relationship between in vitro dissolution rate and in vivo PK performance of pregabalin ER.</td>
<td>330 mg ER (target release) 82.5 mg ER (target release) 330 mg ER (fast release) 330 mg ER (slow release) 330 mg ER (aberrant fast release) 300 mg IR</td>
</tr>
</tbody>
</table>

kcal=kilocalorie; N=number of subjects who received at least 1 dose of study medication; q6=once every 6 h; q12=once every 12 h; QD=once daily; TID=every 6-12 h (eg. 7 AM, 1 PM, 7 PM); PK=pharmacokinetics.

Notes: Meal: low-fat=approximately 15% fat content; medium-fat=approximately 30% fat content; high-fat=approximately 50% fat content.

Source: Summary of Clinical Pharmacology Studies, page 12/61

As Dr. Nallani notes in his review, Pfizer found a large food effect with the LYRICA CR formulation with poor bioavailability in the fasted state. The Applicant addressed this by attempting to optimize the meal size and composition and also examined the timing of the meal with respect to LYRICA CR dosing. The Applicant concluded that the optimal conditions for dosing to address the goals around AUC, C_max, and C_min were to take the dose with the evening meal. Administered with a morning meal, the Test/Reference AUC ratios were in the range of 75-99% but the C_max ratios ranged from 43-44%. When administered with the evening meal, the AUC ratios ranged from 88-103% and C_max ratios from 53-120%.

The clinical pharmacology study warranting further discussion in this review is Study A0081198. This was a randomized, open-label, multiple-dose, crossover study in 24 healthy volunteers. It compared three dosing conditions, LYRICA CR (165 mg x 2 QD), LYRICA CR (330 mg x 1 QD), and Lyrica (150 mg BID). Subjects were dosed for 4 days (LYRICA CR) or 4 ½ days (Lyrica). Lyrica was taken in the fasted condition; LYRICA CR was administered immediately following a medium-fat evening meal containing 600-750 calories. Summary data are presented in tabular form and as a concentration-time figure below.

Descriptive Summary of Plasma Pregabalin PK Parameter Values
The **Cmin** for Lyrica, 150 mg BID in the fasted condition ranges from 1.11 to 1.15 mcg/mL compared to 0.82 and 0.85 mcg/mL for LYRICA CR, 330 mg QD under the optimal administration conditions. The AUCs are comparable, approximately 60 mcg/hr*mL for LYRICA CR compared to approximately 62 mcg/hr*mL for Lyrica. LYRICA CR also generates a lower **Cmax** than Lyrica (4.1 vs. 6.4 mcg/mL).
The key findings from the Clinical Pharmacology program are:

- The bioavailability of LYRICA CR is lower than Lyrica and requires a 10% increase in the nominal dose to match the AUC of the corresponding IR dose.
- Even though Pfizer made that adjustment, Dr. Nallani also notes that Study 1198 showed that three of four partial AUCs (0-6 hrs, 12-18 hrs, and 18-24 hrs) were below the 80% boundary when LYRICA CR was compared to Lyrica.
- The active drug in LYRICA CR is best absorbed when dosed the evening meal.
- Even when dosed the evening meal, the C$_{\text{min}}$ is approximately 25% lower for LYRICA CR than for Lyrica.
- Pregabalin is primarily excreted unchanged in the urine and renal insufficiency increases plasma levels of drug.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical review was conducted by Lisa Wiltrout, MD. The statistical review was conducted by Yan Zhou, PhD with secondary concurrence by David Petullo, MS. Two efficacy studies were conducted and submitted in this application, Studies A0081224 (Study 1224) and A0081245 (Study 1245) in postherpetic neuralgia and fibromyalgia, respectively. Dr. Wiltrout has conducted a detailed and meticulous review of the studies. Please see her review for details.

Briefly, the studies were of similar design (randomized, double-blind, placebo-controlled, parallel-group). Both studies used a randomized withdrawal design having selected patients who responded to LYRICA CR in a six-week single-blind (SB) run in. Pfizer elected to use a primary endpoint of “loss of therapeutic response” (LTR) defined as: less than 30% pain response relative to the SB baseline pain score or patient discontinuation due to lack of efficacy or adverse events. Studies were powered for this endpoint and analyzed in a Kaplan-Meier analysis. Patients meeting randomization criteria (greater than or equal to 50% improvement in pain from SB baseline to end of SB), were randomized to either LYRICA CR or to placebo. Those randomized to placebo were tapered off LYRICA CR over seven days. The double-blind (DB) period of the study lasted 13 weeks. Pain intensity, as measured by an 11-point numerical pain rating scale (NPRS), was reported daily. For Study 1224, the outcome measures beyond the endpoints derived from NPRS included the Brief Pain Inventory, Short Form (BPI), a sleep scale, patient global impression of change, the Short-Form 36 Health Survey (SF36), and similar scales. The FM study used similar outcome measures but also included actigraphy and the Fibromyalgia Impact Questionnaire (FIQ).
Drs. Wiltrout and Zhou both focused their reviews on the landmark analysis of the change from baseline to end-of-study (Week 13) in the weekly mean pain scores and assessed the Applicant’s proposed primary endpoint of LTR as a secondary endpoint. In her review, Dr. Zhou discussed why the Agency requires a statistically significant and clinically meaningful difference in the landmark analysis at 12 weeks or longer. The landmark analysis conducted at 12 weeks detects the difference in pain that occurs late after randomization. The landmark analysis is a surrogate for long-term treatment of chronic pain. On the other hand, the LTR endpoint can detect a difference in pain that occurs early after randomization. Dr. Zhou notes that Pfizer used last observation carried forward (LOCF) to impute missing data which is not acceptable because it wrongly imputes “good” scores for patients who may have experienced pain relief but could not tolerate the drug over 12 weeks. She used a multiple imputation method to account for missing data.

Study 1224 (PHN)

No major issues were identified in study conduct and there was no indication of bias. Randomization resulted in balanced treatment groups. Dr. Zhou’s landmark analysis showed that LYRICA CR is associated with a mean treatment effect size of approximately 1 point. That is a clinically meaningful difference that was statistically significant with a p-value <0.0001. This is summarized in the table below:

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Pregabalin ER vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LS mean</td>
</tr>
<tr>
<td>SB baseline to DB endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin ER</td>
<td>208</td>
<td>-4.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>-3.7</td>
</tr>
<tr>
<td>DB baseline to DB endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin ER</td>
<td>208</td>
<td>0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Source: Dr. Zhou’s review, page 10/22

Study 1245 (FM)

Again, no issues were identified in study conduct or randomization. The summary of the Agency’s landmark analysis follows.

Change in mean daily pain scores at DB endpoint (Week 19) (MI)

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Pregabalin ER vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LS mean</td>
</tr>
<tr>
<td>SB baseline to DB endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin ER</td>
<td>208</td>
<td>-4.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>-3.7</td>
</tr>
<tr>
<td>DB baseline to DB endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin ER</td>
<td>208</td>
<td>0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Source: Dr. Zhou’s review, page 15/22
Dr. Zhou supplemented the tabular data with a figure that shows the average of the imputed and observed pain scores by group over the duration of the double-blind period (Week 7 is the start of double-blind). This is shown below.

**Pain Curves, Study 1245, FM**

*Source:* Dr. Zhou’s review, page 15/22

The primary efficacy endpoint designated by the Applicant was based on the concept of loss of therapeutic response as analyzed with survivor techniques. The Kaplan-Meier curves generated by this analysis are shown below.

**Kaplan-Meier Plot of Time to Loss of Therapeutic Response – DB Phase (FAS Population)**
Pfizer calculated a p-value of \( \text{(b)(4)} \) for the comparison between LYRICA CR and placebo. For the sake of completeness, Dr. Zhou also conducted a Kaplan-Meier analysis and calculated a p-value of \( \text{(b)(4)} \).

So, Study 1245 (FM) \( \text{(b)(4)} \). As described in Dr. Wiltrout’s review, in August 2010, prior to starting Study 1245, the Agency sent an Advice Letter to Pfizer regarding Study 1224. In that letter, Pfizer was advised, \( \text{(b)(4)} \).

To attempt to understand why Study 1245 \( \text{(b)(4)} \), Dr. Wiltrout conducted a thorough analysis of differences between Study 1245 and Study 1224. Dr. Wiltrout concluded \( \text{(b)(4)} \). I agree with Dr. Wiltrout’s assessment and will elaborate upon certain points. I also think that comparisons to Study 1224, the PHN study currently under review, \( \text{(b)(4)} \).
Study 1224, Study Medication Compliance within 1 hour of the evening meal
<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Pregabalin CR SB N=801</th>
<th>Pregabalin CR DB N=208</th>
<th>Placebo DB N=205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>64 (8.0)</td>
<td>14 (6.7)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>80% to 90%</td>
<td>59 (7.4)</td>
<td>10 (4.8)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>&gt;90% to 100%</td>
<td>662 (82.6)</td>
<td>182 (87.5)</td>
<td>185 (90.2)</td>
</tr>
<tr>
<td>&gt;100% to 120%</td>
<td>2 (0.2)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>&gt;120%</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>94.6 (12.49)</td>
<td>95.2 (12.76)</td>
<td>96.5 (10.82)</td>
</tr>
<tr>
<td>Range</td>
<td>4.1 - 102.5</td>
<td>4.1 - 102.5</td>
<td>9.8 - 100.7</td>
</tr>
</tbody>
</table>

Source: Study 1224 CSR, page 104/2533

The proportion of patients with >90% compliance with the dosing regimen was 88% in the PHN study. 

Study 1194 (Epilepsy)

Phillip Sheridan, MD from the Division of Neurology Products was consulted to assess Study 1194, a study in adults with partial onset seizures. Dr. Sheridan notes that the study failed to meet its primary endpoint and that the safety data were consistent with the known adverse event profile of Lyrica.
8. Safety

The safety data submitted in this NDA have been discussed in detail in Dr. Wiltrout’s review. The database consists of the three efficacy studies and 12 Phase 1 studies. Over 1700 subjects and patients received at least one dose of LYRICA CR. No extension studies were conducted so there is essentially no data on exposures over 19 weeks. However, given that the excipients in the new formulation are all qualified and the extensive clinical experience with Lyrica, the safety database is adequate.

The pregabalin molecule has a well characterized adverse event profile with the most common adverse reactions being somnolence, dizziness, blurred vision, weight gain, and peripheral edema. As noted previously, the $C_{\text{max}}, C_{\text{min}}$, and AUC are all comparable or lower for LYRICA CR compared to Lyrica.

There were 3 deaths, 42 serious adverse events (SAEs), and 141 patients treated with LYRICA CR discontinued due to adverse events. Dr. Wiltrout reviewed the major safety findings and I agree that the deaths were unrelated to study drug and the SAEs and events leading to discontinuation were either not related to LYRICA CR or were consistent with the known safety profile of the pregabalin molecule.

There is a formulation-specific safety concern. According to the Applicant, the extended-release mechanism controls the diffusion rate and extends the retention time in the gastric environment. Pfizer states that the gastric retention time is increased by the tablet swelling to exceed the inner diameter of the pylorus. Thus, there is the potential for gastric outlet obstruction with LYRICA CR.

An analysis of formulation-specific safety issues was conducted in two ways. As Dr. Wiltrout describes in her review, she conducted a detailed comparison of the adverse reaction profile both between the studies for which there was a Lyrica and a LYRICA CR study performed and across indications for both formulations. Given that comorbidities vary between patient populations (e.g. epilepsy patients have more adverse events coded as seizures than fibromyalgia patients), Dr. Wiltrout found that the adverse reaction profile was similar between formulations and across indications.

We also submitted an Information Request to the Applicant, requesting adverse event data by system organ class (SOC) and preferred term (PT) to assess the gastrointestinal (GI) adverse events. Two GI SAEs occurred in patients receiving LYRICA CR in the pain studies, coded as gastroesophageal reflux disease and glossitis. There were no cases coded as pyloric or gastric outlet obstruction. Three patients discontinued for nausea and two discontinued for vomiting (n=1242 patients in that dataset). I cannot ascertain whether these cases were mutually exclusive. There is no evidence of formulation-specific safety issues related to the physical properties of the ER formulation.

The package insert for Lyrica indicates that the incidence of euphoria, reported as an adverse reaction, varied between 1% and 12%. In controlled trials of Lyrica, the incidence was 4% for Lyrica versus 1% in placebo. The overall incidence of AEs coded as euphoria in the Phase 3
studies of LYRICA CR was 0.9%. All incidents of euphoria were mild to moderate in intensity and resolved during the studies. At this time, on the basis of the available clinical trial data, there is no evidence that LYRICA CR has a higher abuse liability than Lyrica. Opioids were prohibited in Study 1245 but were permitted in Study 1224. Tramadol was used in a small number (20 [2.5%]) of patients on LYRICA CR in Study 1224.

Pregabalin is a Schedule V drug, defined as having a low potential for abuse. The Controlled Substance Staff (CSS) was consulted to review relevant data in this NDA. CSS has recommended adding two paragraphs to Section 9.1 (Drug Abuse and Dependence/Controlled Substance) of the package insert. The proposed text reads:

Carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA CR misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.

and

Epidemiological studies suggest that pregabalin is being abused for the purposes of obtaining a euphoric effect. These epidemiological studies also show that abuse of pregabalin is more common in individuals who abuse opioids. This type of concomitant abuse can lead to increased mortality. Reserve concomitant use of opioids and Lyrica CR for patients with inadequate alternative treatment options, limit to minimum required dosage and duration.

CSS appears to have based this recommendation on more recent epidemiological studies that show that abuse of pregabalin and gabapentin is increasing, particularly in patients who also abuse opioids, postmarketing data that shows co-prescription of pregabalin with opioids, and data that suggest pregabalin may increase overdose mortality in association with opioids. CSS has also requested postmarketing studies on the abuse of pregabalin with or without concomitant opioids.

CSS requested that the Division of Epidemiology in the Office of Surveillance and Epidemiology (DEPI) conduct a literature search and provide epidemiologic support to the review of this NDA. DEPI assessed drug utilization data, National Poison Data System data, and conducted a literature search to update the Agency’s understanding of the abuse liability of pregabalin and gabapentin. The remainder of this discussion in this review will be limited to pregabalin. Briefly, DEPI found:

1. The total number of prescriptions for pregabalin slightly from \(10^8\) million in 2012 to \(10^9\) million in 2016.
2. An office-based physician survey found that pregabalin was mentioned during office visits with the use of opioid analgesics approximately 19% of the time from which one can infer that significant co-prescribing occurs.
3. With regard to poison control center calls, the number of pregabalin-exposure calls increased sharply after the approval of Lyrica and has remained fairly steady since 2008.

4. There were slight increases in counts of ED visits from 2012 to 2015.

5. The literature suggests that gabapentinoid abuse and misuse is particularly problematic in opioid abusers who use the gabapentinoid to accentuate the effect of the opioid. One study showed that the concomitant ingestion of pregabalin and opioids increases overdose and all-cause mortality in patients on medication assisted therapy.

6. “Overall, post-marketing data do suggest that both [pregabalin and gabapentin] gabapentinoids are abused and misused, particularly among those who abuse or misuse opioids, and those on MAT. These drugs are abused both alone and simultaneously with opioids, and/or other CNS depressants. While the data are limited, as postmarketing research in this area is still in its nascent stages, it is also possible that the abuse or misuse of gabapentinoids is increasing over time.”

DEPI concluded that postmarketing studies should be considered for LYRICA CR and all other pregabalin products as well as enhancing warnings about the risks of misuse, abuse, addiction, overdose, and death.

There are a number of issues with the epidemiology literature that require additional scrutiny before a conclusion can be made. For example, there are no data about the amount of opioids used in the subjects on a gabapentinoid vs. those not on a gabapentinoid. Therefore, the question of whether those with higher opioid demands as part of their OUD are adding additional drugs like the gabapentinoids as a way to supplement their pharmacodynamic effects. Hence, the worse outcomes could reflect higher opioid doses. That does not exclude the possibility that the gabapentinoids contribute to the bad outcomes, but this must be explored further to ensure that labeling for the gabapentinoids does not push prescribers away from one group of non-opioid analgesics that can be useful in many chronic pain patients.

While the evaluation of the extent to which gabapentinoids contribute to overdose and respiratory depression with concomitant opioid use continues, it is premature to add specific warnings about this interaction. The existing warning for interaction with CNS depressants already encompasses this idea, so conscientious prescribers should already be following patients on these drugs more carefully.

9. Advisory Committee Meeting

There were no scientific issues for this reformulated product that required discussion at an Advisory Committee meeting, so no meeting was convened for LYRICA CR.

10. Pediatrics

A pediatric program for LYRICA CR was reviewed in the Pediatric Study Plan (PSP) process. The final Agency decision was that pediatric studies for the indications of PHN, DPN, and FM could be waived because they are unfeasible. I note that Pfizer recently submitted a pediatric study in fibromyalgia for Lyrica that failed to show efficacy.
11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) conducted four clinical investigator inspections that participated in Study 1224. OSI has concluded that Study 1224 was conducted adequately and the data appear acceptable to support the application.

12. Labeling

The proprietary name, LYRICA CR, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). The Patient Labeling Team and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed Medication Guide, Package Insert, and other labeling. Refer to the individual reviews for more details.

Labeling is ongoing at the time of this writing, and specific recommendations have been conveyed in each review. I summarize the key changes from the proposed package insert below.

1. All appropriate sections of labeling will have language related to the use of LYRICA CR for fibromyalgia deleted. The label will include a statement to the effect that efficacy of Lyrica CR in fibromyalgia has not been established.

2. Section 6 of the PI, as submitted in the original NDA, was very detailed and contained information about Lyrica and about indications that will not be approved with this action. Dr. Wiltrout reviewed the adverse reaction profile between formulations and across indications and found that the events reasonably attributable to pregabalin were consistent across formulation and indication. Thus, the Adverse Reactions section was substantially truncated and simplified.

3. As discussed in Section 8 of this review, at this time, I recommend against adding the two paragraphs proposed by CSS. Dr. Sharon Hertz, DAAAP Division Director has addressed this with CSS and DEPI.

4. Consistent with other recently approved drugs for chronic pain, we replaced the for Study 1224 with a continuous responder analysis.

5. The labeling must include some language about the failed studies in epilepsy and FM.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The peripheral neuropathic pain indications, PHN and DPN, may be approved. The FM indication should receive a Complete Response action.
Risk Benefit Assessment

CDPR

Given that the Agency reasonably allowed the Applicant to leverage data that it owns from Lyrica, Pfizer submitted substantial evidence of efficacy for postherpetic neuralgia which can be extrapolated to painful diabetic neuropathy. The study submitted was a randomized, double-blind, parallel-group study that was able to demonstrate a statistically significant, clinically meaningful difference in pain intensity at 13 weeks. The fibromyalgia study failed to show a benefit on the landmark analysis. The safety data from the clinical development program were consistent with the known adverse event profile for the pregabalin moiety. The risk-to-benefit relationship is positive for PHN and DPN. FM because no efficacy was demonstrated.

Deputy Division Director

I agree with Dr. Shibuya’s assessment that the Applicant has demonstrated that the benefit of Lyrica CR outweighs the risk for the neuropathic pain indications (PHN and DPN), based on the results of the study conducted in PHN. The fibromyalgia study failed to demonstrate efficacy using the landmark analysis, which is the Division’s acceptable analysis for chronic pain indications. Therefore Lyrica CR will be approved for PHN and DPN, but not fibromyalgia.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

At this time, I do not recommend any postmarketing study(ies) or a REMS. New data pertaining to the abuse liability of pregabalin will continue to be reviewed by the Agency.

Recommendation for other Postmarketing Requirements and Commitments

As above.

Recommended Comments to Applicant

Per the Biopharmaceutics review, the following should be conveyed to the Applicant.

In order to have a better quality control of your product, we believe an additional dissolution time point at 9 hours is necessary. Following the approval of the NDA, we recommend that you submit dissolution data (at release and stability) for all the batches at 1 hour, 4 hours, 9 hours and 24 hours. We also recommend that you propose acceptance criteria at each time point for the Agency to review and make a final decision on the dissolution acceptance criteria for future batches.
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
10/11/2017

ELLEN W FIELDS
10/11/2017