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APPLICATION NUMBER:

021446Orig1s028

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 20, 2012
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA # **Supplement #**	21446 028
Applicant Name	PF PRISM CV, a Division of Pfizer Inc.
Date of Submission	December 20, 2011
PDUFA Goal Date	June 20, 2012
Proprietary Name / **Established (USAN) Name**	Lyrica/ pregabalin
Dosage Forms / Strength	Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg Oral Solution: 20 mg/mL
Proposed Indication	Management of Neuropathic Pain Associated with Spinal Cord Injury
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL	Frank Pucino, Pharm.D., M.P.H.
CMC	Bartholome Ho, Ph.D., James Vidra, Ph.D.
Environmental Assessment Review	Raanan A. Bloom, Ph.D, Nakissa Sadrieh, Ph.D.
Clinical Pharmacology	Srikanth Nallani, Ph.D., Yun Xu, Ph.D.
Controlled Substance Staff	Silvia Calderon, Ph.D., Michael Klein, Ph.D.
OSI	Lauren Iacono-Conner, Ph.D., Janice Pohlman, M.D., Susan Cummins, M.D., M.P.H.
OPDP	Sam Skariah, Pharm.D., Lisa Hubbard, Pharm.D., L. Shenee Toombs, Pharm.D., Shefali Doshi, M.D.
OMPI	Latonia Ford, Ph.D., Barbara Fuller, R.N., M.S.N., C.W.O.C.N.
Project Management	Diana Walker, Ph.D., Parinda Jani

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMPI=Office of Medical Policy Initiatives

1. Introduction

Pfizer submitted this supplement in support of a new indication for the gamma-aminobutyric acid analog Lyrica, for the management of neuropathic pain associated with spinal cord injury. Lyrica has already been approved in this division for the management of the pain of three other conditions: postherpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), and fibromyalgia (FM). It has also been approved by the Division of Neurology Products as adjunctive therapy for adult patients with partial onset seizures.

2. Background

Neuropathic pain associated with spinal cord injury (NP-SCI) has been reported to occur in as many as 40% of patients after spinal cord injury. This pain can be severe and disabling, and there are no approved products for the treatment of NP-SCI. Indeed, there are very few unapproved drugs that provide any clinically significant analgesia for these patients currently available. Therefore, as this new indication clearly

addresses an unmet medical need, this supplementary application was reviewed on a priority time line.

The Applicant has submitted the results of two adequate and well-controlled clinical trials of Lyrica in patients with NP-SCI, in addition to data from a long-term, open-label safety study and the 28-week interim data from a second long-term safety study. The only additional new information submitted with this supplement is an environmental assessment (EA).

3. CMC

Based on their review of the submitted data, Drs. Bloom and Sadrieh have concluded the following, as reproduced from page 3 of their review:

> Based on FDA EA guidance and an evaluation of the information provided in this and the previous EA for Lyrica®, no further testing is required and no adverse effects are expected from the introduction of pregabalin into the environment due to the use of Lyrica®.

I concur with the review team that there are no outstanding CMC issues that would impact approvability.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were submitted with this application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data were submitted with this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The Applicant submitted the results of two adequate and well-controlled clinical trials to demonstrate the efficacy of Lyrica in patients with NP-SCI.

Study 125

This was a 14-week (1-week baseline phase, 3-week dose titration phase, 9-week fixed-dose maintenance phase, 1-week to follow up visit), randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with all study sites located in Australia. Subjects were started on 150 mg (divided BID) per day or placebo, and titrated to a target dose range of 150 to 600 mg per day. The subjects had a diagnosis of traumatic SCI of at least one-year duration with central neuropathic pain that had persisted continuously for at least three months or with remissions and relapses for at least 6 months. Subjects must have had a baseline pain score of at least 4 on an 11-point numerical rating scale (NRS) and a pain score of at least 40 mm on the 100 mm VAS of the Short-Form-McGill Pain Questionnaire. The primary efficacy outcome was a comparison of the weekly mean pain intensity (PI) score over the last seven days while on study drug measured on an 11-point NRS. The Applicant analyzed this using an analysis of covariance with baseline pain score as a covariate. Since the Applicant included baseline pain as a covariate, the analysis of the "endpoint mean score" mimics an analysis of the "change from baseline," our standard for analgesic studies. However, we generally prefer the change from baseline to Week 12. The Applicant's analysis of the "endpoint mean score" evaluated the change from baseline to the last 7 days. The last 7 days may not have necessarily been during Week 12 for each patient. For example, a patient's last 7 diary entries may have occurred during Week 3 and then the patient dropped out. In this case, the Week 3 scores were then carried forward. Therefore, this analysis was analogous to an LOCF approach for imputing missing data. Mr. Petullo reanalyzed the data using more conservative imputation strategies and still found a statistically significant treatment effect. The results of his analysis are reproduced below as summarized by Dr. Pucino, from page 17 of Dr. Pucino's review:

Agency's Primary Efficacy Analysis (Study 125)

Imputation	Treatment	N	Mean Pain Intensity (SE)			
			Baseline	WeeK12	Change	p-value
BOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.1)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.2 (0.2)	< 0.001
mBOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.2)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.3 (0.2)	< 0.001

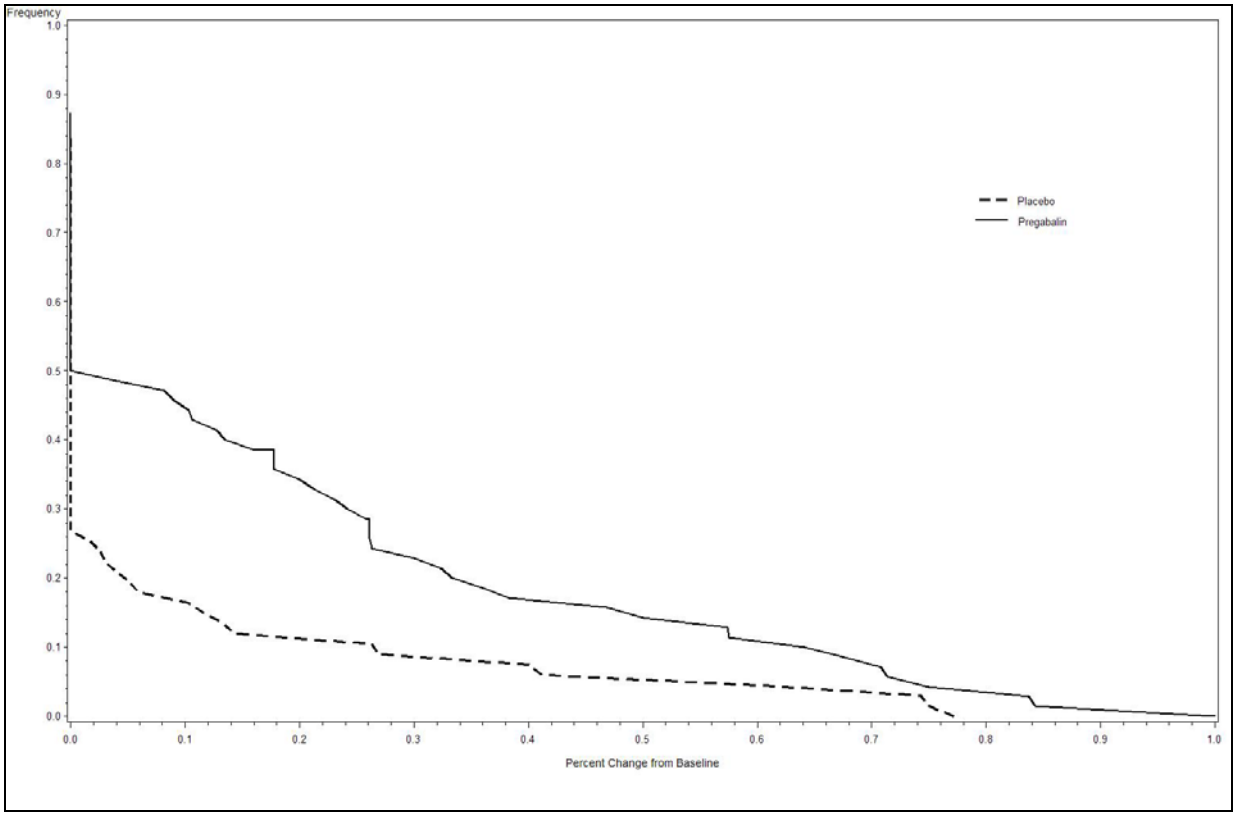
Source: Adapted from Mr. Petullo's Statistical Review, Tables 1 and 2, p 7.

The Applicant's secondary outcome measure analyses were generally supportive of the primary outcome, but were not corrected for multiplicity and do not provide any

compelling evidence of additional benefits beyond the analgesic effect demonstrated by the primary outcome.

Mr. Petullo also performed a continuous responder analysis which demonstrates a clear separation of the curves with a statistically significant difference between the curves employing both the Van der Waerden test and the Wilcoxon Ranks Sum test. This curve is reproduced below from page 18 of Dr. Pucino's review:

Continuous Responder Analysis Curves Using BOCF (Study 125)



Source: David Petullo's Statistical Review, Figure 1, p. 10.

Study 1107

This was an 18-week (4-week dose-adjustment phase, 12-week fixed-dose maintenance phase, 1-week taper phase, 1-week to follow up phase), randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with study sites located in multiple countries, including 18 in the US. Subjects were started on 150 mg (divided BID) per day or placebo, and titrated to a target dose range of 150 to 600 mg per day. The subjects had to have Bryce-Ragnarsson SCI Type 14 or 15 neuropathic pain. The primary outcome measure was the duration adjusted average change (DAAC), defined as the difference between the baseline pain score and the mean of all post-baseline pain

scores, adjusted by the proportion of the planned study duration completed by the subject. This endpoint may have attributed some treatment benefit to patients that withdrew for adverse events. Thus, the statistical team reanalyzed it using "change from baseline to Week 16" and employed BOCF as the imputation strategy. The results of Mr. Petullo's analysis are summarized in the table below, reproduced from page 23 of Dr. Pucino's review:

Reviewer's Primary Efficacy Analysis (Study 1107)

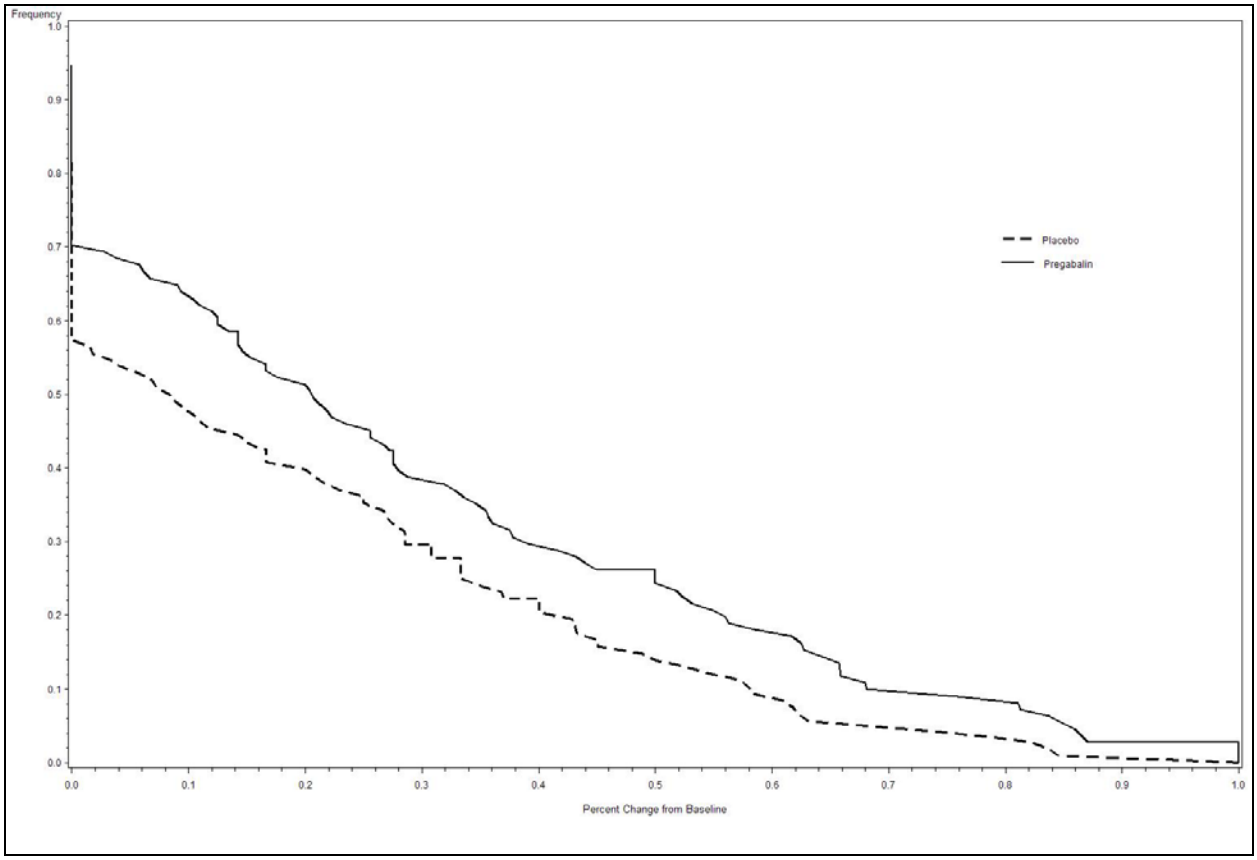
Imputation	Treatment	N	Mean Pain Intensity (SE)				
			Baseline	Wk16	Change	Diff	p-value
BOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.014
mBOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.015

Source: Mr. Petullo's Statistical Review, Tables 13, p 7.

The Applicant's secondary outcome measure analyses were generally supportive of the primary outcome, but do not provide any compelling evidence of additional benefits beyond the analgesic effect demonstrated by the primary outcome.

Mr. Petullo also performed a continuous responder analysis which demonstrates a clear separation of the curves with a statistically significant difference between the curves employing both the Van der Waerden test and the Wilcoxon Ranks Sum test. This curve is reproduced below from page 24 of Dr. Pucino's review:

Continuous Responder Analysis Curves Using BOCF (Study 1107)



Source: David Petullo's Statistical Review, Figure 2, p. 16.

I concur with the clinical and statistical review teams that the Applicant has provided substantial evidence of efficacy for Lyrica in the treatment of NP-SCI.

8. Safety

The following table, reproduced from page 27 of Dr. Pucino's review, summarizes the exposure safety database for the clinical development program:

Summary of Clinical Trials Used to Evaluate Safety in the NP-SCI Clinical Developmental Program

Study	Design	Treatment Duration	Treatment	Randomized (n)
Completed Controlled Trials				
125	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	12 Weeks	Lyrica 150-600 mg/d	70
			Placebo	67
1107	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	17 Weeks	Lyrica 150-600 mg/d	112
			Placebo	107
Completed Open-Label Extension Trial of Study 125				
202	Open-label	9 Months	Lyrica 150-600 mg/d	**103***
Total Number of Patients Exposed to Lyrica : 235				

Cumulative Exposure in Controlled and Uncontrolled NP-SCI Trials

	Number of Subjects						
	Total Daily Dose of Lyrica (mg/day)						
Duration of Exposure	**>0 to <75**	**75 to <150**	**75 to <150**	**150 to <300**	**450 to <600**	**≥ 600**	**Any Dose**
<24 Wks	0	137	211	187	119	97	151
≥24 Wks to <36 Wks	0	0	6	8	2	3	8
≥36 Wks to <52 Wks	0	0	4	5	3	0	8
≥52 Wks to <104 Wks	0	0	10	9	6	11	27
≥104 Wks to <156 Wks	0	0	3	4	4	15	34
≥156 Wks	0	0	1	0	0	0	7

*53 Placebo-treated patients enrolled into Study 202 from Study 125 were treated with Lyrica.
Source: Adapted from Applicant's response to information requested in the Filing Letter (dated 3/9/2012), p 2.

There was a single death in the open-label extension study (Study 202) which was reported as being due to progression of metastatic cancer. I concur with the clinical review team that this death was unlikely to be related to exposure to Lyrica.

All of the serious adverse events and adverse events leading to discontinuation were either consistent with the known safety profile of Lyrica or deemed to be unrelated to

exposure to Lyrica by the clinical review team. The common adverse events were also consistent with the well-established safety profile of Lyrica. Somnolence, however, was observed more frequently (36%) in the SCI patient population than had been observed previously in other populations (12% to 28%). Dr. Lloyd further evaluated this finding and summarized his conclusions as reproduced from page 110 of his review:

> The Applicant analyzed the frequency of somnolence in the controlled CNP-SCI population with respect to concomitant benzodiazepines. Among pregabalin-treated subjects, the frequency of somnolence was 46.6% in subjects who took concomitant benzodiazepines compared to 30.6% in subjects who did not take these medications. Similarly, the frequency of somnolence among placebo-treated subjects who took concomitant benzodiazepines was 15.4% compared to 9.2% in those who did not take these medications. The ratio between the frequency of CNP-SCI subjects in the pregabalin group and placebo groups with somnolence was 3.1, which was comparable to the diabetic peripheral neuropathy/postherpetic neuralgia population (3.6). This ratio was 2 in the adult partial onset seizure population and 5 in the fibromyalgia population.
>
> Concomitant benzodiazepine use only partly explains the higher frequency of somnolence seen in the CNP-SCI population as its frequency among pregabalin treated subjects ***not*** taking concomitant benzodiazepines is higher than its frequency among pregabalin treated subjects for other approved indications. However, the comparable ratios between populations suggests that the phenomenon is attributable to some aspect of the population rather than study drug alone.
>
> Other potentially sedating concomitant medications, particularly when taken in combination, and factors related to the underlying disease process could also contribute to the higher frequency of somnolence in the CNP-SCI population. Potentially sedating concomitant medications (e.g., baclofen, opioids, amitriptyline, and oxybutynin), in addition to benzodiazepines, were commonly used by subjects in the pregabalin and placebo groups.

This finding will be incorporated into the product labeling. I concur with the review team that there were no concerning safety signals documented during this development program that would result in an unfavorable risk-benefit balance.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting as there were no unusual concerns for this new patient population regarding the efficacy or safety of this approved and widely prescribed analgesic drug product.

10. Pediatrics

Pediatric studies were not required for this application and the Applicant was granted a full waiver for performing pediatric studies as the number of children with this

condition is so small as to make a clinical study infeasible. The Pediatric Review Committee reviewed and concurred with this decision.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The Division and the Applicant have reached agreement on appropriate changes to the product label for this new indication and safety database. There were no areas of major disagreement.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has provided data from adequate and well-controlled studies to support the efficacy and safety of Lyrica for the management of neuropathic pain associated with spinal cord injury. The only new safety finding was a higher incidence of somnolence in this population which, while associated with Lyrica exposure, is also to a large degree associated with the other drugs commonly used in this patient population that have sedation as a side effect. The benefits of Lyrica in providing analgesia in this extremely disabling and difficult to treat condition far outweigh any risks associated with its chronic use, when prescribed for appropriate patients and according to the product labeling.

- Postmarketing Risk Management Activities
  None.

- Postmarketing Study Commitments or Requirements
  None.

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/s/

BOB A RAPPAPORT
06/20/2012