

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-488

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 31, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Carlos M Mena-Grillasca, RPh, Team Leader
Denise Toyer, Pharm D, Deputy Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name(s): Lyrica (Pregabalin) Oral Solution
20 mg/mL

Application Type/Number: NDA 022488

Applicant/sponsor: Pfizer

OSE RCM #: 2009-1083

1 INTRODUCTION

This review is in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products to evaluate the container label and insert labeling for the product Lyrica Oral Solution (NDA 22-488), for areas that could lead to medication errors. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2009-1083 dated November 23, 2009 and December 8, 2009. All our previous recommendations on the Lyrica Oral Solution container labels and carton labeling have been addressed with the exception of the insert labeling revisions to the Pregabalin Dosage Adjustment Based on Renal Function Table (i.e. Renal Dosing Table).

2 CONCLUSIONS AND RECOMMENDATIONS

The current “Dosage Adjustment Based on Renal Function Table” resulted in confusion leading to medication errors. Thus, the Applicant and the Agency have been working together to revise the proposed table to ensure that the complex dosing information for all the different indications of use is clear and will not result in medication errors once it is introduced into the insert labeling. To ensure that the revised table does not introduce more confusion we recommend the Applicant perform a Usability Study prior to implementation. The objective of the study is to demonstrate that health care professionals who prescribe and dispense Lyrica can interpret the information presented in the table and accurately dose a patient with renal impairment. In addition, the Usability Study should verify a level of understanding that makes the occurrence of medication errors unlikely. We encourage the Applicant to submit a draft Usability Study protocol for our review and comment prior to the initiation of the study.

We acknowledge that the PDUFA date for the Lyrica Oral Solution NDA is January 4, 2010. Therefore, DMEPA recommends keeping the currently approved Renal Dosing Table in the insert labeling for the action on this NDA. The Applicant should continue working with the Agency in the near future to address the Usability Study and implementation of an improved Renal Dosing Table through a Prior Approval Supplement.

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

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/s/

CARLOS M MENA-GRILLASCA
12/31/2009

DENISE P TOYER
12/31/2009



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 15, 2009

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA 22-488 Lyrica (Pregabalin)

Indication: Treatment for neuropathic pain associated with diabetic neuropathy, and management of postherpetic neuralgia, epilepsy (adjunctive therapy for partial onset seizures in adult patients), and fibromyalgia

Dosages: 20 mg/mL oral solution

Company: Pfizer Inc. for CP Pharmaceuticals Internationals C.V.

Materials received: NDA 22-488 (March 4, 2009) is located in the EDR
CSS consult from March 24, 2004
OSE consult from Sep 2, 2009

This memorandum responds to a consultation from the Division of Anesthesia, Analgesia and Rheumatology Products regarding the abuse potential of oral solution of Lyrica (pregabalin). FDA approved Pregabalin in 2005 as Lyrica® for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for partial onset seizures in adult patients), and fibromyalgia. Pregabalin is marketed as a hard capsule for oral use (25 to 300 mg). It is considered to have a low potential for abuse, and is thus classified as a Schedule V drug in the U.S.

The Sponsor submitted a new NDA 22-488 for an oral solution of Lyrica which was developed for patients who have difficulty swallowing capsules. The Sponsor requested a biowaiver which was granted; pregabalin is considered a Class 1 compound with high solubility and high permeability. Sponsor did not submit any new clinical data; therefore, this evaluation of abuse

potential is based solely on the review of DAWN and AERS data for the marketed product in US during the years 2005-2009.

I. EXECUTIVE SUMMARY

CONCLUSIONS

At the present time CSS notes a signal of abuse of undetermined strength, as indicated by review of the data from AERS and DAWN. Because of the potential for the drug to cause euphorogenic effects in certain populations, pharmacovigilance is indicated.

RECOMMENDATIONS

CSS recommends that the sponsor conduct routine pharmacovigilance of the drug and report all cases of abuse and misuse, by formulation. The sponsor should submit a summary of analysis in three years of all available data (including DAWN and AERS) from the US market for both formulations: capsules and oral solution.

II. BACKGROUND INFORMATION

1. Product description

The final commercial product is a clear, colorless solution of pregabalin 20 mg/mL, containing the sweetening agent, sucralose, and artificial strawberry flavor. The solution is buffered to approximately pH 6.1 and includes also a preservative system of methylparaben and propylparaben.

2. Pharmacological profile

In the central nervous system, pregabalin binds to the $\alpha 2\delta$ (alpha2delta) subunit of the voltage-dependent calcium channel and reduces depolarization-induced calcium influx with a consequential modulation in excitatory neurotransmitter release ¹.

3. Abuse potential of the drug during clinical trials

During clinical development of the drug pregabalin under NDA 21-466, euphoria was seen as an adverse event. In fact, during the phase 2 and 3 studies, a high rate of euphoria was reported by Generalized Anxiety Disorder (GAD) patients taking pregabalin in clinical trials: 11.8% in the 450 mg group, 10.3% in the 200 mg group and 4.8% in the 400 mg group. In contrast, the placebo-treated rate of euphoria in GAD patients was 1.2%.

In addition, the reported incidence of euphoria from pregabalin was 1.0-2.4% in neuropathic pain patients and 1.0-2.2% epilepsy patients, at doses of 150, 300 and 600 mg, relative to the incidence in the placebo-treated groups (0.0% in neuropathic pain patients and 0.3% in epilepsy patients).

4. Evaluation of abuse potential of the marketed product

¹ Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia*. 2004;45 Suppl 6:13-8. Review.

CSS Consult: NDA 22-488 Lyrica (Pregabalin)

An Office of Surveillance and Epidemiology consult to evaluate the potential abuse of the marketed drug product Lyrica (pregabalin) during years 2005-2009 indicated a total of 1252 in AERS with 289 reports of adverse events indicative of potential abuse, overdose, and euphoria associated with pregabalin. The AEs were grouped into three categories: 1) Drug abuse (n=156, 12.4%), 2) Overdoses (n=74, 5.9%) and 3) Euphoria (n=72, 5.7%). The Drug abuse category included the following preferred terms: intentional drug misuse, drug withdrawal syndrome, drug dependence, drug abuse, drug tolerance, and drug abuser, and polysubstance dependence. The category of Overdoses included preferred terms such as: accidental overdose, intentional overdose, multiple drug overdose, and multiple drug overdose intentional.

Additionally, CSS identified abuse related terms including hallucinations (n=17), confusional state (n=23), thinking abnormal (n=10), feeling abnormal (n=48) and feeling drunk (n=6).

The majority of AEs reported by AERS belonged to the category “serious”.

The Drug Abuse Warning Network was also searched and showed a total of 2116 non-medical use emergency department visits during the years 2005-2009 associated with pregabalin.

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

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/s/

ALICJA LERNER
12/15/2009

LORI A LOVE
12/15/2009

MICHAEL KLEIN
12/15/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 8, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Lyrica (Pregabalin) Oral Solution
20 mg/mL

Application Type/Number: NDA 022488

Applicant: Pfizer

OSE RCM #: 2009-1083

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products for a review of the revised Lyrica container label in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2009-1083 dated November 23, 2009.

2 MATERIAL REVIEWED

The Applicant provided the revised label on December 7, 2009. We also evaluated the recommendations pertaining to the previous revision in OSE review #2009-1083.

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2009-1083. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised container label submitted by the Applicant adequately addresses our concerns from a medication error perspective.

If you have further questions or need clarifications, please contact Abolade Adeolu, OSE Project Manager, at 301-796-4264

1 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CC /TS)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL
CORP

LYRICA (PREGABALIN)

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/s/

Latoya S TOOMBS
12/08/2009

DENISE P TOYER
12/08/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 30, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Carlos M. Mena-Grillasca, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: LaToya Sheneé' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Measuring Device Review

Drug Name(s): Lyrica (Pregabalin) Oral Solution
20 mg/mL

Application Type/Number: NDA 022488

Applicant/sponsor: Pfizer

OSE RCM #: 2009-1083

1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products to evaluate the need for the Sponsor to provide a measuring device for the product Lyrica Oral Solution (NDA 22-488).

2 DISCUSSION

DMEPA evaluates the need for a measuring device in a case by case basis considering the proposed product profile (e.g. usual dose, safety profile, etc.) and the implications of using household measuring devices (e.g. teaspoons or tablespoons), with varying precision, in dosing and administering the product.

The usual doses for Lyrica can range from 25 mg (1.25 mL) to 600 mg (30 mL). All doses in this range can be measured using standard oral measuring devices. Since there is a wide range of potential doses based on the Dosage and Administration section of the labeling, it may prove difficult for the Sponsor to provide a device that accommodates all doses. In addition, there are no instances (i.e. titration, renal adjusted dosing, etc.) that would require unusual volumes that would not be measurable using standard oral measuring devices.

Based on discussions from the clinical review team, there are no specific dose related safety concerns that may result from minor variations introduced by the use of standard oral measuring devices.

3 CONCLUSIONS AND RECOMMENDATION

DMEPA concludes that based on the Lyrica Oral Solution product profile, it is not necessary for the sponsor to provide an oral measuring device with this product.

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NDA-22488	ORIG-1	PFIZER CHEMICAL CORP	LYRICA (PREGABALIN)

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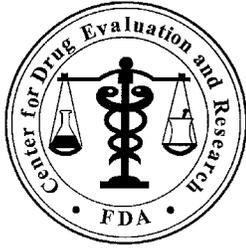
/s/

Latoya S TOOMBS
12/02/2009

CARLOS M MENA-GRILLASCA
12/02/2009

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CAROL A HOLQUIST
12/02/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 23, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Carlos M. Mena-Grillasca, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Lyrica (Pregabalin) Oral Solution
20 mg/mL

Application Type/Number: NDA 022488

Applicant/sponsor: Pfizer

OSE RCM #: 2009-1083

1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products to evaluate the container label and insert labeling for the product Lyrica Oral Solution (NDA 22-488), for areas that could lead to medication errors.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the Lyrica Oral Solution container label and insert labeling received May 29, 2009 (see Appendix A).

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

The proposed product is a new oral solution formulation of the currently marketed product, Lyrica, (NDA's 21-446, 21-723 and 21-724). Lyrica is currently available as 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules. Since Lyrica is already marketed, we searched AERS to determine the medication error profile of Lyrica. A search of the AERS database was conducted using the High Level Group Terms (HGLT) 'Medication Errors', and 'Product Quality Issues', with the search criteria of 'Pregabalin' (active ingredient), 'Lyrica' (tradename), and verbatim terms of 'Lyr%'.

The cases were manually reviewed to determine if medication errors occurred. Cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors that might be applicable to the review of the proposed labels and labeling.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT (ORAL SOLUTION)

The concentration of the oral solution is presented as '20 mg per 1 mL'.

The route of administration is presented as 'Not for Parenteral Use'.

The container label lacks a place to document the open date for the bottle.

The package insert contains a conversion table from mg to mL.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.2 MEDICATION ERROR CASES

The AERS Database search retrieved a total of 352 reports. Three hundred and eleven reports were eliminated from further analysis for the following reasons.

- Foreign reports (113). These reports did not indicate label and labeling, or nomenclature as a source of error.
- Adverse events (66) including weight gain, insomnia, blurred vision, dizziness, etc., which were not the result of medication errors.
- Patients taking concomitant medications that lead to mental status changes, excessive drowsiness, etc (37)
- Drug Overdoses due to intentional and accidental exposure. The reports of accidental exposure involved children accidentally ingesting the drug (26)
- Product quality complaints and lack of efficacy reports (25)
- Dose omission due to patients forgetting or missing doses, in some cases due to adverse events (22)
- Suspect drug was not Lyrica (16)
- Wrong Patient (3)
- Intentional wrong route of administration (1)
- Expired drug dispensed (1)
- Zyrtec ordered and erroneously transcribed on the MAR as Lyrica in June 2007 (1)

The remaining forty-one cases involved improper doses (34) and the use of the wrong technique (7) when administering Lyrica

3.2.1 IMPROPER DOSE (N=34)

Thirty cases describe the administration of an incorrect dose due to patient misinterpretation of physician's instructions, patient self-titration, physicians prescribing higher than recommended starting doses, nursing maladministration due to lack of appropriate MAR notation, and one case of dispensing the wrong strength. (150 mg dispensed instead of 50 mg; causality not indicated). DMEPA's review of these cases did not identify any label and labeling vulnerabilities that could be attributed to these medication errors. In the latter case DMEPA reviewed the container labels for the 50 mg and 150 mg strengths, and concluded they were adequately differentiated. Thus, regulatory action is not warranted for these thirty improper dose cases. The remaining four cases are described below.

3.2.1.1 Improper Dose in Renal Impaired Patients (n=3)

Two of the improper dose cases described overdoses to renal impaired patients. Both patients were admitted to the hospital with altered mental status changes, and received pregablin doses higher than the daily recommended dosages. Pregabalin was discontinued in both patients. In one case the patient received dialysis and recovered. In the other case the symptoms resolved but no other outcome information was noted. No causality was reported; however in one case the reporting pharmacist noted the dosage information for renal patients presented in the package insert was not clear and recommended revision of the dosing table.

In the remaining case a pharmacist cited concerns that the renal dosage recommendations for Lyrica are presented in a very confusing manner. Specifically she stated, “Since BID or TID means Twice Daily or Three Times daily respectively, you wouldn’t realize that Pfizer created their own definition which is BID=two DIVIDED doses or TID=three DIVIDED doses.”

3.2.1.2 Lack of Instruction on Patient Samples (n=1)

One case described a patient receiving samples of pregabalin that did not contain instructions. The reporter did not indicate if instructions were given by the provider. The patient took the medication and experienced insomnia, leg numbness and cramping and subsequently discontinued the medication. It can not be determined if the adverse events occurred due to lack of instruction on the patient samples. No outcome information was noted.

DMEPA notes Lyrica has four indications with varying dose recommendations and titration schedules. Due to limited spacing on the sample container labels, display of this information in a concise and organized manner would be difficult. Additionally, providing the various dosage recommendations for each indication may also result in confusion and thus medication errors due to dosing information not specific for a patient’s indication, being presented on the sample. Our review of the container labels and labeling submitted by the sponsor March 10, 2005 (NDA 21-723) note that a “Usual Dosage: See package insert for dosage information” statement is included on the physician sample labeling.

3.2.2 WRONG TECHNIQUE (N=7)

Seven cases describe patients opening the capsules and ingesting the enclosed contents. The patients described various reasons for opening the capsules. These include the desire to decrease the dose as a result of adverse events, self-tapering in order to discontinue the medication, the inability to swallow whole capsules and the desire to avoid ingestion of the animal-origin gel capsules. Although adverse events were reported we were unable to determine if these adverse events were a result of patients using the wrong technique during administration. None of these cases indicated that the patients were instructed by their healthcare practitioners to open the capsules.

4 DISCUSSION

Our assessment of the Lyrica Oral Solution container labels, insert labeling and post-marketing medication errors identified two areas of concern that can be improved upon. These include 1) confusing renal dosage recommendations and 2) confusing information on the labels and labeling.

4.1 Confusing Renal Dosage Recommendations (*Reference Current Renal Dose Table 1*)

Lyrica is approved for four different indications of use, each with varying starting doses, maximum daily dosages and frequency of administration. Our analysis of the insert labeling revealed that the dosing recommendations for patients with normal renal function for each indication are independently detailed in separate sections of the Dosage and Administration section. In contrast, the dosage recommendations for renal impaired patients for all indications are combined into one table (see below).

Column 1

Column 2

Column 3

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Row 1 →

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
	≥60	30-60	15-30	<15	
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50-75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

† Supplementary dose is a single additional dose.

When prescribing a dose for renal impaired patients, Table 1 is confusing because a practitioner must first identify the daily dose for a patient with normal renal function for the applicable indication of use, which is located in a separate section of the Dosage and Administration section. Next, practitioners have to find this dose in Table 1 under the Total Pregabalin Dose (see Column 2 and Row 1). The practitioner then identifies the patient’s creatinine clearance and must read across that row, until they are in the column corresponding to the normal pregabalin daily dose previously identified. Once they have identified the reduced dose, they must continue reading across the row to column 3 titled “Dose Regimen” to find the appropriate frequency of administration. After completing these steps, the dose they have identified is the total daily dose which must be given in one, two or three divided doses. However, in Column 3 the Applicant uses the abbreviations BID and TID which may lead the prescriber to think the total daily dose should be administered two or three times daily instead of dividing the daily dose accordingly. One postmarketing medication error cited the inappropriate use of BID and TID in this column as being confusing. It is our determination that the Applicant’s attempt to consolidate the renal impaired dosing information in one table is confusing to practitioners and error prone.

Additionally, Table 1 contains recommendations for supplemental dosing post-hemodialysis. However, the supplemental dosing appears to provide conflicting information which is outlined below.

- Supplemental doses are generally indicated to replace the eliminated amount of drug during dialysis, but this table recommends that the same amount or more be given, without guidance.

- The table also provides overlapping supplemental dosing recommendations for each strength. For example a patient on a routine daily dose of 25 mg may be given a supplemental dose of 25 mg, 50 mg, or 75 mg. However, the table does not contain any guidance as to which dose (i.e., 25 mg, 50 mg, or 75 mg) should be chosen.
- Generally, for patients undergoing dialysis while receiving medications that are dialyzed, doses are held until after dialysis. However, the table does not discuss holding doses of Lyrica or what to do with the supplemental dose if the normal dose is held.

There is a lot of pertinent and frequently referenced information presented in this table that should be revised so that it is presented clearly and concisely. Relocating the renal dosing recommendations under each indication in the Dosage and Administration section, will minimize the number of different sections that practitioners may use to calculate a renal dose and will eliminate the need for a combined table.

4.2 Lack of ‘Swallow Capsules Whole’ Statement

Six medication error cases indicated that patients opened the Lyrica capsules in order to decrease their available dose as a result of adverse events, self-tapered in order to discontinue the medication, inability to swallow capsules whole and the desire to avoid ingestion of animal-origin gel capsules. Review of the container labels and patient information section of the insert labeling noted that there is no statement warning patients to not open the capsules, and swallow the product whole. Informing patients that they should not open the capsules to take partial quantities of the medication will minimize the potential for improper technique errors.

4.3 Presentation of Product Strengths

The concentration of the oral solution is currently presented as ‘20 mg per 1 mL’. The number ‘1’ which appears before ‘mL’ can be misinterpreted as 10 mL. This presentation is problematic and may lead to an erroneous calculation by the health care practitioner. For example, if ‘20 mg per 1 mL’ is interpreted as ‘20 mg per 10 mL’, an overdose will occur.

4.4 Route of Administration

The route of administration is presented as ‘Not for Parenteral Use’. Statements such as ‘Not for Parenteral Use’, ‘Not for Inhalation’, and ‘Not for Injection’ may inadvertently encourage wrong routes of administration due to the reader’s focus on the route of administration and overlooking the word ‘not’. Statements should appear in a positive tone such as “For Oral Use Only”.

4.5 Lack of Date Opened Space

The container label lacks a place to document the open date for the bottle. The addition of this area will allow the user to keep track of the 45 day expiration once the bottle is opened.

4.6 Milligram per Milliliter Conversion Table

The package insert contains a conversion table from mg to mL. Although this table was included to facilitate the accuracy in dosing of the oral solution, it may encourage prescribers to prescribe using volume (milliliters) instead of the dose (milligrams). This may provide a source of confusion and medication errors.

5 RECOMMENDATIONS

Our evaluation of the proposed container label and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 5.1 *Comments to the Division* for discussion during the labeling meetings. Section 5.2 *Comments to the Applicant* contains our recommendations for the container label. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

5.1 COMMENTS TO THE DIVISION

A. TITLE HEADING

The current presentation of the Control symbol (i.e. CV) may be confusing and could be interpreted as part of the official name for the product. Revise this symbol using the standard presentation of the controlled substance designation. (e.g. the Roman numeral “V”, enclosed with in the capital letter “C”). 

B. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. DOSAGE AND ADMINISTRATION

- a. Add the statement, “Lyrica is given orally with or without food” to be consistent with the Full Prescribing Information Dosage and Administration section.
- b. Add the statement, “Swallow capsules whole” to address post-marketing reports of patients opening the capsule to take half or partial doses.
- c. Add the statement, “When discontinuing Lyrica, taper gradually over a minimum of 1 week to be consistent with the Full Prescribing Information Dosage and Administration section.
- d. Remove the reference to the Conversion Table. (see comment B.3)

C. FULL PRESCRIBING INFORMATION

1. DOSAGE AND ADMINISTRATION- Section 2

- a. Add the statement, “Swallow capsules whole” to address post-marketing reports of patients opening the capsule to take half or partial doses.
- b. Patients with Renal Impairment- Section 2.5
 - i) To avoid misinterpretation of dosage recommendations for renal impaired patients, delete the separate section for Patients with Renal Impairment including the Dosage Adjustment table as currently

presented (Section 2.5) and include the renal dosage recommendations under the corresponding indication of use section (e.g. Section 2.1).

- ii) Provide specific guidance on the supplemental dose recommendations (For example, if a patient is taking 25 mg once daily, the supplemental dosage recommendations are 25 mg, 50 mg or 75 mg. Also include what considerations should be considered before a dose is selected and are there recommendations for holding a dose until after dialysis.)

c. Conversion Table- Section 2.6

Delete this section from the insert labeling. Although this table was included to facilitate the accuracy in dosing of the oral solution, it may encourage prescribers to prescribe using volume (milliliters) instead of the dose (milligrams). This may provide a source of confusion and medication errors.

2. HOW SUPPLIED/STORAGE AND HANDLING- Section 16

For consistency between the container label and insert labeling, add the statement, “Use within 45 days of first opening the bottle”. This information is provided on the container label, however there is no supporting reference in the insert labeling.

3. PATIENT INFORMATION

Add the statement, “Swallow capsules whole” to address post-marketing reports of patients opening the capsule to take half or partial doses.

4. MEDICATION GUIDE

Add the statement, “Swallow capsules whole” to address post-marketing reports of patients opening the capsule to take half or partial doses.

5.2 COMMENTS TO THE APPLICANT

A. General Comments

This product includes a medication guide and can be dispensed as a unit-of-use or in multiple uses. Ensure the quantity is sufficient to provide each patient with a medication guide.

B. Container Label (Oral Solution)

1. Revise the concentration (20 mg per 1 mL) to read, “20 mg per mL”.
NOTE: Delete ‘1’ prior to ‘ml’.
2. Revise the statement, “Each 1 mL contains 20 mg of pregabalin”, to read “Each mL contains 20 mg of pregabalin”.
3. Revise the statement, “NOT FOR PARENTERAL USE” to read “FOR ORAL USE ONLY”.
4. Revise the statement, “DOSAGE AND USE...information” to read “Usual Dosage: See package insert for dosage information.”

5. Increase the prominence and relocate the statement “Use within 45 days of first opening the bottle” to the top of the side panel to ensure that the user is aware that once the bottle is opened the product must be used within 45 days.
6. To allow the user to keep track of the 45 day expiration, provide a space to write the date the bottle is first opened.

Appendix A: Container Label



Appendix :B Pregabalin Dosage Adjustment Based on Renal Function

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
	150	300	450	600	
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

† Supplementary dose is a single additional dose.

APPENDIX C: MEDICATION ERROR CASES

Receipt Date CASE #	Type of Error	Abbreviated Narrative
Improper Dose – Prescribing Error (n=3)		
5/24/2007 5336703-4	Improper Dose	Patient admitted with mental status changes, falling, ataxia, and dysarthria which had progressed over past 2 months since starting pregabaliln for severe peripheral neuropathy. He was admitted for management and symptoms resolved with discontinuation of medication. Of note, his est. Clcr =30 ml/min so recommended dose of pregabalin would be 300 mg/day. Patient was prescribed 600 mg/day.
9/21/2007 5466616-9	Improper Dose	An 85-year old female was admitted to teaching hospital. She was hypoxic, and had altered mental status changes over the past month while in nursing home. Her medications from the nursing home were reviewed by pharmacist. She was on Lyrica 50 mg po twice daily for peripheral neuropathy. However she had renal failure and was receiving dialysis. It was noted that her dose should have been 25-75 mg po daily. During hospitalization, pregabalin was held and she was dialyzed. She recovered. The pharmacist wanting to know how to dose Lyrica for patients with renal failure, reviews the package insert via the internet, and notes the information was listed in a table format, but was not clear. There were 3 columns for dosing, under the heading “Total Pregabalin Daily Dose (mg/day). It was clear that the renal failure patients should be dosed daily, but it was not clear about how many milligrams, since there were 3 options.
08/16/2006 5081500-0	Improper Dose	This case involved a report of potential medication error due to the renal dosage recommendations. The information is presented in a very confusing manner. BID or TID means Twice Daily or Three times daily respectively, you wouldn’t realize that Pfizer created their own definition which is BID=two DIVIDED doses or TID=Three DIVIDED doses.
Improper Dose – Lack of Instruction on Patient Samples (n=1)		
5/07/2009 6182064-0	Improper Dose	A 46 year old female reports that she began on pregabalin unknown dose for fibromyalgia. On an unknown date she received samples of pregabalin from her physician which did not contain instructions. While on an unknown dose she was not able to sleep.
Wrong Technique (n=7)		
9/28/2005 4784397-9	Wrong Technique	This consumer reports that his 52 year old wife started taking Lyrica (pregabalin) 100 mg daily for interstitial cystitis pain on 12Sep2005. The patient was also taking Elavil, Seroquel, Oxycontin and clonazepam for pain management. On 12Sep2005, five to six hours after taking her first dose of Lyrica, the patient took her other pain medications and one-half hour later, the patient experienced trouble driving home and staggered from the car. The patient was found passed out sitting at the kitchen table after a couple of hours. When the patient was revived, she was groggy, her speech was mumbled and she did not have the strength or energy to move. The patient stated that she could not walk straight and felt overdosed from the pain medications. The patient chose not to go the hospital and by the next morning, on 13Sep2005, she was improved except she had scratched the cornea of her eye and she felt a pounding pressure in her head. The patient continued to take Lyrica , but opened the capsule and only took an estimated one-fourth of the contents. Since 13Sep2005, the patient continues to feel groggy and feels the pressure in her head. Like it was pounding. The Lyrica was obtained in the USA.
8/25/2008 5856690-X	Wrong Technique	This consumer reports that her currently 79 year old husband began treatment with Lyrica for neuropathy about 2 years ago. Relevant medical history includes in a wheelchair, can hardly walk, heart attack, very little small intestine, and has to have all his medicines crushed. It is unknown if there is relevant past drug history or concomitant medications. She reports that she opens the capsule, crushes the medicine and puts it in his food. She does this for all of his medicines. The Lyrica has worked well for him and she has not had any problems. He has not had problems with weight gain while taking Lyrica. It is unknown if there is relevant laboratory data. The Lyrica is continued and was obtained in the US. Follow-up(18Jun2008): This consumer reports that her husband has had 54 inches of small intestine removed and in addition he

		has an ileostomy; it is unknown if this was before or since Lyrica was started. The capsules come out whole described as can actually read "Pfizer" on them. Follow up (13Aug2008): The physician reports no new information. He wants to know "what's the problem?"
5/23/2006 5010682-1	Wrong Technique	This currently 59 year old female consumer, with a history of headaches and feeling sleepy and groggy, reports that she started taking Lyrica on 17Apr2006 for nerve pain. Beginning on 17Apr2006, the patient took Lyrica 75 mg nightly for days with planned increases to 75 mg twice daily for thereafter. On 21Apr2006, after taking Lyrica for four days, the patient stopped taking it due to experiencing shooting pain in her arms and legs, more often when in bed at night. After starting Lyrica, the sleepiness and grogginess worsened and she could not function. While on the Lyrica the patient noticed that her headaches had stopped and after stopping Lyrica, her headaches returned. On 01May2006, the patient restarted Lyrica, but decreased her dose by opening the capsule and taking half of the capsule nightly. The headaches, grogginess, and sleepiness resolved. As of 07May2006, the patient continues to take Lyrica. Additional concomitant medications include Bextra, which she continued to take until she ran out of medication.
9/06/2006 5099812-3	Wrong Technique	This 55-year old female consumer reported to a Pfizer product manager about being treated in Aug2006 with Lyrica (pregabalin) 75 mg twice daily for approximately one week for back pain. In Aug2006, the consumer started to experience abrupt sneezes (she doesn't manage to get her hand to cover her nose on time), sensations of pins and needles in the arm, increased blood glucose and heavy flatulence. The consumer is recovering from the events and she will continue the treatment because the effect of Lyrica has been excellent. Follow-up information is not available. During the phone call the consumer stated that she is going to open the capsule and only ingest the content in order to avoid the gelatin of animal origin.
6/27/2006 5042075-5	Wrong Technique	This 46-year old female, on an unknown date, about four months ago, started on Lyrica 25 mg three times daily for polyneuropathy. After starting Lyrica, people would ask her if she felt hot because she would be flushed. After taking Lyrica for a few months, she experienced problems breathing, chest pain, nausea and vomiting. On an unclear date, apparently after starting Lyrica, she did experience night sweats and "malaria like symptoms". On an unknown date in 2006, about two weeks ago, her Lyrica was increased to 50 mg three times daily to try to get her pain under better management because she was in a panic because she seemed to have more pain and be more tender. It is unclear if the increased dose improved her pain and tenderness. She wants to stop Lyrica for unclear reasons and asked a pharmacist who told her to just stop, but she did not feel she should stop suddenly. On an unknown date, she started opening her Lyrica 50 mg capsules and removed about half of the contents (or even a little more), then re-closed the capsule. She states part of the reason she wants to stop Lyrica is that it does not seem to help her pain but she did not elaborate on any other reasons for wanting to stop. As of 15 Jun2006, she is still taking Lyrica but it is unknown what dose she is taking.
10/18/2008 5923008-3	Wrong Technique	A 51 year old female reports swelling up very badly like her whole body was pressurized which got worse while taking Lyrica 50 mg two times a day. Her dose was reduced to 25 mg two times a day due to the above mentioned events. She further complains of several adverse events, including increased anxiety, interfered sleep, nausea, headache, lack of concentration, ringing in ears, etc., while taking Lyrica 25 mg two times a day. Due to the above mentioned events she took half of 25 mg Lyrica by opening the capsule.
08/28/2006 5092513-7	Wrong Technique	A 56 year-old male started on Lyrica in November 2005 for neuropathic pain. On unknown dates Lyrica caused dizziness, nausea, diarrhea, or loose stools, occasional blurred or double vision, forgetfulness, loopy, weight gain, etc. Patient then started to taper off his dose of Lyrica to see if he still had the neuropathic pain- he didn't think he needed Lyrica anymore, and started to taper by decreasing his total daily dose by 25 mg every week but thinks he was tapering too quickly; he has tried taking a "half of a 50 mg capsule" so he doesn't have to purchase the 25 mg capsules of Lyrica. During the tapering of Lyrica he has experienced nausea, headaches, dizziness, diarrhea, etc.

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

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/s/

Latoya S TOOMBS
11/23/2009

CAROL A HOLQUIST
11/24/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 10, 2009

To: Bob A. Rappaport, M.D., Director
**Division of Anesthesia, Analgesia and Rheumatology
Products (DAARP)**

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)
LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): LYRICA (pregabalin) Oral Solution

Application
Type/Number: NDA 22-488

Applicant/sponsor: Pfizer, Inc.

OSE RCM #: 2009-1082

1 INTRODUCTION AND BACKGROUND

This review is written in response to a request by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Lyrica (pregabalin) Capsule and Oral Solution Medication Guide (MG) submitted on May 29, 2009. A MG-only REMS for NDA 22-488 for Lyrica (pregabalin) Capsules was approved on April 23, 2009. The Applicant has proposed to add the oral solution formulation information to the currently approved Lyrica Capsules MG.

2 MATERIALS REVIEWED

- Draft Lyrica (pregabalin) Capsules and Oral Solution Prescribing Information (PI) submitted May 29, 2009 and revised throughout the review cycle
- Draft Lyrica (pregabalin) Capsules and Oral Solution Medication Guide (MG) submitted May 29, 2009 revised throughout the review cycle
- Approved Lyrica (pregabalin) Capsules Medication Guide (MG) for NDA 22-488 dated April 23, 2009

3 RESULTS OF REVIEW

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

15 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL
CORP

LYRICA (PREGABALIN)

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/s/

ROBIN E DUER
11/10/2009

MARY E WILLY
11/10/2009
I concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: November 10, 2009

To: Diana Walker – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-488 Lyrica (pregabalin) Oral Solution C-V

DDMAC has reviewed the proposed Medication Guide for Lyrica (pregabalin) Oral Solution C-V (Lyrica), submitted for consult on March 10, 2009.

The following comments are provided using the updated proposed Medication Guide sent via email on November 3, 2009 by Diana Walker. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

Comments on the proposed product labeling (PI) were provided in a separate memo on November 5, 2009 by Mathilda Fienkeng.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL
CORP

LYRICA (PREGABALIN)

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/s/

TWYLA N THOMPSON

11/10/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: November 5, 2009

To: Diana Walker – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-488 Lyrica (pregabalin) Oral Solution C-V

DDMAC has reviewed the proposed product labeling (PI), and container labeling for Lyrica (pregabalin) Oral Solution C-V (Lyrica), submitted for consult on June 12, 2009.

The following comments are provided using the updated proposed PI sent via email on November 4, 2009 by Diana Walker. DDMAC has reviewed the proposed container labeling and has no comments. If you have any questions about DDMAC's comments, please do not hesitate to contact us

Comments on the proposed Medication Guide will be provided in a separate memo by Twyla Thompson.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL
CORP

LYRICA (PREGABALIN)

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/s/

MATHILDA K FIENKENG

11/05/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 9/2/09

To: Michael Klein Ph.D., Director
Controlled Substance Staff

Through: Lauren Choi Pharm. D., Team Leader
Division of Pharmacovigilance II
Office of Surveillance and Epidemiology
Martin Pollock, Pharm. D., Safety Evaluator
Division of Pharmacovigilance II
Office of Surveillance and Epidemiology

Subject: Drug abuse-related events

Drug Name, Application
number and Sponsor Pregabalin, NDA 21446; 21723; 21724; CP Pharms

OSE RCM #: 2009-1168

EXECUTIVE SUMMARY

The Controlled Substance Staff requested that OSE provide U.S. AERS (Adverse Event Reporting System) crude count reports of abuse, overdose, and euphoria associated with pregabalin. The AERS search revealed 289 reports from 2005-2009. A separate SOC/PT listing, which contains a listing of all CNS-related events for the 289 reports is also enclosed.

1 BACKGROUND

The CSS (Controlled Substance Staff) is reviewing an NDA (22-488) for pregabalin solution and expressed concerns regarding the known abuse potential of the drug. Pregabalin is a (DEA) schedule V product and was approved on 12/30/04 for neuropathic pain and seizures. CSS requested that we provide domestic AERS crude counts of abuse-related events, overdose, and euphoria associated with pregabalin.

2 METHODS

An AERS database was searched for U.S. reports with pregabalin as a suspect drug, from time of marketing (9/7/05) to 6/26/09. The MedDRA terms used in the search are listed in Table 1.

Table 1. MedDRA terms used in AERS search

Event Description	MedDRA Term	MedDRA Hierarchy
Drug abuse	Drug tolerance	PT
	Drug abuse	
	Drug dependence	
	Intentional drug misuse	
	Polysubstance dependence	
	Drug withdrawal syndrome	
	Drug withdrawal headache	
	Drug withdrawal convulsions	
	Drug withdrawal syndrome neonatal	
	Withdrawal arrhythmia	
	Drug abuser	
	Ex-drug abuser	
	Maternal use of illicit drugs	
	Substance abuser	
	Drug tolerance increased	

Event Description	MedDRA Term	MedDRA Hierarchy
	Tachyphylaxis	
Overdoses	Overdoses ¹	HLT
Euphoria	Euphoric mood	PT

For the ‘other CNS’ events, an AERS standard SOC-PT listing was prepared.

3 RESULTS

The AERS database retrieved 289 domestic reports. Table 2 shows the distribution of the reported events.

Table 2. Distribution of crude AERS reports of selected events (n=289)^{2,3}

Drug abuse	156
<i>Preferred terms</i>	
Drug abuse	21
Drug abuser	5
Drug dependence	31
Drug tolerance	8
Drug withdrawal syndrome	52
Intentional drug misuse	57
Polysubstance dependence	1
Overdoses	74
<i>Preferred terms</i>	
Overdose	45
Accidental overdose	11
Intentional overdose	8
Multiple drug overdose	7

¹Contains the following PT's: Overdose. Accidental overdose, Intentional overdose, Multiple drug overdose, Multiple drug overdose accidental, and Multiple drug overdose intentional.

²A single report can have more than one PT.

³Some PTs are listed in Table 1 but not in Table 2. This means that there were no reports for these particular PTs.

Multiple drug overdose intentional	3
Euphoria	72

The data for 'other CNS' events for the 289 reports is contained in the AERS standard report (*Cases by Primary SOC and PT*) below:



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DISCLAIMER FOR STANDARD AERS REPORTS

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering these figures, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors which influence reporting, comparisons of drug safety cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It also should be noted that in some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, these data were generated using computer printouts, and some of the numbers may reflect duplicates.

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/s/

MARTIN L POLLOCK
09/03/2009

LAUREN Y CHOI
09/03/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: NDA 22-488

Name of Drug: Lyrica (pregabalin) Oral Solution, 20 mg/mL

Applicant: CP Pharmaceuticals International C.V.

Agent for Applicant: **Pfizer, Inc.**

Material Reviewed:

Submission Date(s): March 4, 2009

Receipt Date(s): March 4, 2009

Submission Date of Structure Product Labeling (SPL): March 4, 2009

Type of Labeling Reviewed: WORD

Background and Summary

LYRICA® (pregabalin) Oral Solution, which was developed for patients who have difficulty swallowing capsules, is a new dosage form of pregabalin and will have the same indications as LYRICA (pregabalin) Capsules, as approved in NDA 21-446, and the 21-723 and 21-724 efficacy supplements. The label submitted March 4, 2009, with this new NDA 22-488 was reviewed for PLR format and was also compared to the approved label for Lyrica Capsules, dated June 21, 2007. This review will not be a content comparison review.

Review

The label was found to be identical in format to the approved label. Only information on the new dosage form was added (as this is not a content comparison review, these additions will not be delineated). In addition, this label was found to conform to PLR guidelines.

The following issues/deficiencies have been identified in the proposed labeling: NONE.

Recommendations

No changes to the label format are recommended. The label is ready for content review by the NDA review team.

Reviewer:

Diana L. Walker, PhD
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

Drafted: DWalker/08Apr09

Revised/Initialed: PJani/10Apr09

Finalized: DWalker/10Apr09

CSO LABELING REVIEW OF PLR FORMAT

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/s/

Diana Walker
4/10/2009 11:11:27 AM
CSO

Parinda Jani
4/15/2009 09:57:29 AM
CSO