

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-488

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-488	Submission Date(s): 03/04/2009
Brand Name	LYRICA
Generic Name	Pregabalin
Clinical Pharmacology Reviewer	Suresh B Narahariseti, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Pfizer Inc
Relevant IND(s)	-
Formulation; Strength(s)	Oral Solution, 20 mg/mL
Indication	Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia
Proposed Dosage Regimen	The daily dose volume for patients is expected to be up to 30 mL (600 mg pregabalin).

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1. Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Pfizer Inc. submitted NDA 22-488, Lyrica (pregabalin) Oral Solution, 20 mg/mL under section 505 (b) (1) of the Federal Food Drug and Cosmetic Act. On December 30, 2004 Lyrica capsules under NDA 21-446 was approved for neuropathic pain, epilepsy and management of fibromyalgia. This new pregabalin dosage form is for identical indications as those of Lyrica capsules, and is intended for patients who have difficulty in swallowing capsules.

No new clinical pharmacology information was submitted in this NDA. Pregabalin has been determined to be a Biopharmaceutical Classification System (BCS) Class 1 compound with high solubility/high permeability characteristics (see Clinical Pharmacology review for NDA 21-446 by Dr. Sue Chih Lee dated 3/22/04 for additional details on this aspect and other relevant Clinical Pharmacology information). Since this is a solution dosage form, it meets the rapidly dissolving criteria as well. The biowaiver request for this oral solution NDA was assessed by ONDQA and waiver has been granted. Please see review dated 08/04/2009 by Dr. John Hill of ONDQA

The sections relevant to clinical pharmacology in the sponsor submitted product label are shown in Section 3. No Clin Pharm related labeling changes are proposed by the sponsor and are not proposed by this reviewer either.

Overall, the submitted information is acceptable from a clinical pharmacology perspective.

2 QBR

2.1 General Attributes

Pfizer Inc. submitted NDA 22-488, Lyrica (pregabalin) Oral Solution, 20 mg/mL under section 505 (b) (1) of the Federal Food Drug and Cosmetic Act. On December 30, 2004 Lyrica capsules under NDA 21-446 was approved for neuropathic pain, epilepsy and management of fibromyalgia. This new pregabalin dosage form is for identical indications as those of Lyrica capsules, and is intended for patients who have difficulty in swallowing capsules. No new clinical pharmacology or Clinical information was submitted in this NDA. Instead, sponsor is seeking the approval of this oral solution based on BCS Class I criteria.

2.2 General Clinical Pharmacology

Pregabalin meets the criteria for a BCS Class-1 compound and hence no new clinical pharmacology information was submitted in this NDA. The pharmacokinetics, and bioavailability studies characterized in the original NDA 21-446 are applicable to this product as

well. Please refer to Clinical Pharmacology review for NDA 21-446 by Dr. Sue Chih Lee dated 3/22/04 for additional details. The sections relevant to clinical pharmacology in the sponsor submitted product label are shown below in Section 3. No new Clin Pharm related labeling changes were proposed by the sponsor and no changes are forthcoming from this reviewer either.

2.3 Intrinsic Factors

2.3.1 Pediatric plan.

The current Lyrica oral solution is being developed as a new dosage form of pregabalin and is intended for use in approved indications in adult patients who may require or benefit from the convenience of an oral solution (e.g., difficulty swallowing oral capsules). The original Lyrica capsules NDA- 21-446 was approved for the following four indications.

- (1) neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- (2) postherpetic neuralgia (PHN)
- (3) adjunctive therapy for patients with partial onset seizures
- (4) fibromyalgia

Pfizer proposed that the ongoing pediatric assessments for the capsule formulation sufficiently address requirements under PREA and therefore requests a full waiver of further pediatric assessment for the oral solution.

The PeRC at the agency met on 09/14/09 and the following considerations were made: Full waiver for indications (1) and (2) and partial waiver and/or deferral for selected pediatric subpopulations for indications (3) and (4). Following is a brief summary of these:

(a) Pediatric age groups to be waived: for the reason that studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed).

- (1) neuropathic pain associated with diabetic peripheral neuropathy (DPN) - ages 0-16 years.
- (2) postherpetic neuralgia (PHN) – ages 0-16 years.
- (3) adjunctive therapy for patients with partial onset seizures – ages 0-1 month.
- (4) fibromyalgia – ages 0-12 years.

(b) Pediatric age groups deferred:

- (3) adjunctive therapy for patients with partial onset seizures – ages 0-1 month.

There is already an ongoing pediatric epilepsy program for patients aged 1 month to 16 years with Lyrica capsules and these studies are applicable to the Lyrica Oral Solution. The pediatric epilepsy program is in Phase 1. There are four Phase 3 trials scheduled to begin once data is available from Phase 1. A summary plan of all of the studies has been submitted. An age appropriate oral formulation has been developed and submitted under IND 76,815 on December 21, 2006.

- (4) fibromyalgia- ages 13 to 16 years.

There is already an ongoing pediatric fibromyalgia program for patients aged 13 to 16 years with Lyrica capsules and these studies are applicable to the Lyrica Oral Solution. As a postmarketing commitment associated with the approval of management of fibromyalgia

indication in June 2007 (NDA 21-446; S-010), a pediatric fibromyalgia study in adolescent patients (ages 13 to 16) was required under PREA. The final report submission is due by 31 January 2012. This study will be conducted under IND 66,902 (fibromyalgia).

2.4 Extrinsic Factors

Not Applicable

2.5 General Biopharmaceutics

Pregabalin has been determined to be a Biopharmaceutical Classification System (BCS) Class 1 compound with high solubility/high permeability characteristics. The biowaiver request for this oral solution NDA has been granted and is exempt from typical in vivo bioavailability/bioequivalence studies. Please refer to the review dated 08/04/2009 by Dr. John Hill of ONDQA

2.6 Analytical

Not Applicable

3 Labeling

Sections relevant to clinical pharmacology in the submitted product label:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the α_2 -delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the α_2 -delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA_A, GABA_B, or benzodiazepine receptors, does not augment GABA_A responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

12.3 Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of LYRICA capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is $\geq 90\%$ and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CL_{cr}) [*see Dosage and Administration, (2.5)*].

12.4 Pharmacokinetics in Special Populations

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of LYRICA were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and LYRICA drug exposure is similar between genders.

Renal Impairment and Hemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CL_{cr}). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified [*see Dosage and Administration (2.5)*].

Elderly

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CL_{cr}. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function [*see Dosage and Administration, (2.5)*].

Pediatric Pharmacokinetics

Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions

In Vitro Studies

Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. In vitro drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP 3A4 substrates (e.g. midazolam, testosterone) is not anticipated.

In Vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18

healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive

Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine

Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
<i>Concomitant drug has no effect on the pharmacokinetics of pregabalin</i>	
Hypoglycemics	Glyburide, insulin, metformin
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
<i>Concomitant drug has no effect on the pharmacokinetics of</i>	

Therapeutic class	Specific concomitant drug studied
	<i>pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug</i>

Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
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4 Appendix

4.1 Annotated Proposed labeling



(b) (4)

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

4.2 Individual Study Reviews

Not Applicable

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
<u><i>General Information About the Submission</i></u>				
	Information		Information	
NDA/BLA Number	22488		Brand Name	LYRICA
OCP Division (I, II, III, IV, V)	II		Generic Name	Pregabalin
Medical Division			Drug Class	
OCP Reviewer	Suresh B Narahariseti		Indication(s)	Diabetic peripheral neuropathy, neuralgia, adjunct therapy for epilepsy
OCP Team Leader	Suresh Doddapaneni		Dosage Form	Oral Solution
Pharmacometrics Reviewer			Dosing Regimen	Beginning dose 150 mg/day (2-3 times a day)
Date of Submission	03/04/2009		Route of Administration	Oral
Estimated Due Date of OCP Review			Sponsor	Pfizer Inc
Medical Division Due Date			Priority Classification	
PDUFA Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1	1	Pediatric plan
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				

Bio-waiver request based on BCS	X	1		
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	1	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	BCS-Class 1
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES. Sponsor is requesting a BCS Class I based biowaiver for this solution formulation. During the course of the review of NDA 21-446 (Lyrica Capsules), pregabalin was determined to be a BCS Class I drug.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Suresh Babu Naraharisetti

April 1, 2009

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni

April 1, 2009

Team Leader/Supervisor

Date

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH B NARAHARISSETTI
11/05/2009

SURESH DODDAPANENI
11/05/2009

Biopharmaceutics Review

NDA:	22-488
Submission Date:	March 4, 2009
Type of Submission:	Original New Drug Application
Product name:	Pregabalin
Trade Name:	Lyrica®
Dosage Form:	Oral Solution
Dosage Strengths:	20 mg/mL
Sponsor:	Pfizer

Recommendation

Pregabalin meets the criteria for a Biopharmaceutical Classification System (BCS) Class-1 compound, which is exempt from typical in vivo bioavailability/bioequivalence studies. The formulation did not change since the agreement which was given by DNP on 1 August 2007. Therefore, the biowaiver request is granted.

Background

Pregabalin has analgesic, anxiolytic, and anticonvulsant activity. Pregabalin is currently approved as Lyrica® for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia. Pregabalin is currently marketed as a hard capsule dosage form for oral use (25 to 300 mg).

LYRICA® (pregabalin) oral solution was developed for patients who have difficulty swallowing capsules. It is a new dosage form of pregabalin which will have the same indications as LYRICA (pregabalin) capsules.

The oral solution concentration was selected at 20 mg/mL for dosing flexibility. The daily dose volume for patients is expected to be up to 30 mL (600 mg pregabalin).

The sponsor is planning to register the pregabalin oral solution formulation by biowaiver which was supported by the previous agreements between the FDA and the sponsor achieved at the 07 June 2000 meeting and subsequently confirmed on 01 August 2007.

Assessment

Pregabalin is a highly soluble and permeable molecule, which dissolves and is absorbed rapidly in the gastrointestinal tract. Therefore, pregabalin meets the criteria for a Biopharmaceutical Classification System (BCS) Class-1 compound, which is exempt from typical in vivo bioavailability/bioequivalence

studies. Also, registration by biowaiver is supported by the previous agreements between the FDA and the sponsor achieved at the 07 June 2000 meeting. In summary, agreements from that meeting included the following points pertinent to the oral solution:

- Based on the draft BCS (finalized in 2003), pregabalin is considered a Class 1 compound (high solubility/high permeability)
- At a given strength and series (family of compositionally proportional formulations), the quality control dissolution data adequately confirm bioequivalence across formulations.
- Pregabalin dissolution data demonstrates that all immediate release formulations used in clinical trials are rapidly dissolving (>85% dissolved in 30 minutes).
- Comparisons of dissolution profiles of representative formulations demonstrate bioequivalence of all clinical formulations. For example: the low and high strength (25 and 150 mg) formulations of Series A and the low and high strength (75 and 300 mg) formulations of Series C are bioequivalent to 100 mg Series B formulation.

On 16 May 2007, the sponsor submitted a letter to Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) and Division of Neurology Products (DNP) advising them that Pfizer planned to proceed with the biowaiver agreement that took place at the June 2000 meeting specific to bioequivalence between formulations as the basis for submission of an application for approval of the oral solution. Pfizer requested confirmation from the FDA that submission of the NDA for the oral solution was consistent with Pfizer's interpretation of the previous agreements.

On 26 July 2007 DNP requested that Pfizer confirm the ingredients and respective quantities for the oral solution formulation. Pfizer confirmed these details by email on 26 July 2007. Pfizer received an email on 1 August 2007 from DNP confirming that a biowaiver would be in effect for the LYRICA oral solution. The Division indicated that the biowaiver would be granted per the ingredients and amounts provided to them on 26 July 2007. Please see below 1 August 2007 email from DNP granting Pfizer an oral solution biowaiver.

Please see the response from the PK team below:

A Biowaiver can be granted for the liquid pregabalin formulation given below (provided to us upon request).

Item #	Component Grade	Concentration (mg/mL)
1	Pregabalin (API) Pharm	(b) (4)
2	Methylparaben NF	(b) (4)
3	Propylparaben NF	(b) (4)
4	Sodium Phosphate, Monobasic, Anhydrous USP	(b) (4)
5	Sodium Phosphate, Dibasic, Anhydrous USP	(b) (4)
6	Sucralose NF	(b) (4)
7	Artificial Strawberry #11545 n/a	(b) (4)
8	Purified Water (Total) USP	(b) (4)
	TOTAL	(b) (4)

If any major changes are made to the formulation then the review Division should be consulted again.

Knowing the formulation is important before the biowaiver can be granted because excipients can sometimes affect the rate and extent of drug absorption. Large quantities of certain excipients, such as surfactants (b) (4) and sweeteners (b) (4) may be problematic, hence the reviewer wanted to know the ingredients and their quantities. Please refer to the FDA guidance on Biowaivers using BCS.

Table 1 below shows the unit formula included in 4 March 2009 submission. The quantitative composition is not different from what was agreed upon in the above e-mail.

Table 1: Quantitative composition of pregabalin oral solution, 20 mg/ml

Component	Function	Reference to Standards ¹	Unit Formula (mg/mL)
Pregabalin	Active	In house standard	20.0
Methylparaben (methyl parahydroxybenzoate)	Preservative	NF ² or Ph. Eur. ³	(b) (4)
Propylparaben (propyl parahydroxybenzoate)	Preservative	NF or Ph. Eur.	
Monobasic sodium phosphate anhydrous	(b) (4)	USP ⁴	
Dibasic sodium phosphate anhydrous		USP or Ph. Eur.	
Sucralose	Sweetener	NF	
Artificial Strawberry Flavor #11545	Flavor	N/A ⁵	
Purified Water	(b) (4)	USP or Ph. Eur.	

¹ Relevant compendial grade testing will be used in each region (for example, USP/NF for US region, Ph. Eur. for EU region)

² NF = National Formulary

³ Ph. Eur. = European Pharmacopoeia

⁴ USP = United States Pharmacopoeia

⁵ N/A = Not Applicable

(b) (4)

(b) (4)

Comments

Pregabalin meets the criteria for a Biopharmaceutical Classification System (BCS) Class-1 compound, which is exempt from typical in vivo bioavailability/bioequivalence studies. The formulation did not change since the agreement which was given by DNP on 1 August 2007. Therefore, the biowaiver request is granted.

Houda Mahayni, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.

Biopharmaceutics Expert
Office of New Drug Quality Assessment

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22488	----- ORIG 1	-----	----- LYRICA (PREGABALIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOUDA MAHAYNI
08/03/2009

PATRICK J MARROUM
08/04/2009

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22488	Brand Name	LYRICA
OCP Division (I, II, III, IV, V)	II	Generic Name	Pregabalin
Medical Division		Drug Class	
OCP Reviewer	Suresh B Narahariseti	Indication(s)	Diabetic peripheral neuropathy, neuralgia, adjunct therapy for epilepsy
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Oral Solution
Pharmacometrics Reviewer		Dosing Regimen	Beginning dose 150 mg/day (2-3 times a day)
Date of Submission	03/04/2009	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Pfizer Inc
Medical Division Due Date		Priority Classification	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS	X			
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	BCS-Class 1
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate	X			

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES. Sponsor is requesting a BCS Class I based biowaiver for this solution formulation. During the course of the review of NDA 21-446 (Lyrica Capsules), pregabalin was determined to be a BCS Class I drug.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Suresh Babu Naraharisetti
Reviewing Clinical Pharmacologist

April 1, 2009
Date

Suresh Doddapaneni
Team Leader/Supervisor

April 1, 2009
Date

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suresh Naraharisetti
7/15/2009 11:51:59 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/17/2009 04:44:45 PM
BIOPHARMACEUTICS