Office of Clinical Pharmacology Review

NDA or BLA Number	021446 S32
Link to EDR	\\cdsesub1\evsprod\NDA021446\0173
Submission Date	02/29/2016
Submission Type	*[Standard]*
Brand Name	Lyrica Oral Capsules and Oral solution
Generic Name	Pregabalin Oral Capsules and Oral solution
Dosage Form and Strength	Oral Capsules: 25 – 300 mg Oral Solution: 20 mg/mL
Route of Administration	Oral
Proposed Indication	Fibromyalgia
Applicant	Pfizer Inc.
Associated IND	*[IND66902]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D. and Kevin Krudys, Ph.D.]*
OCP Final Signatory	*[Kevin Krudys, Ph.D., and Yun Xu, Ph.D.]*

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective and the PMR is considered fulfilled. The sponsor should include appropriate labeling, described below, in the pediatric population.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Pfizer submitted an efficacy supplement comprising of postmarketing requirement (PMR) final clinical study report for Pediatric efficacy study A0081180 "A 15-week, randomized, doubleblind, parallel-group, placebo-controlled flexible-dose safety and efficacy study of pregabalin in adolescents (12-17 years old) with fibromyalgia." Pfizer also submitted labeling to incorporate results of this PMR study. Pfizer had agreed to conduct this pediatric PMR study at the time of approval of Lyrica for the indication of fibromyalgia on 21 June 2007. LYRICA oral solution was approved on 04 January 2010 (NDA 22488), and also included the requirement for postmarketing pediatric assessment under PREA to evaluate the safety and efficacy of pregabalin for FM patients 13 years of age and older. Agency granted a partial waiver for children 12 years of age and younger. The submitted study was also a PMR for the NDA 22488 (pregabalin oral solution).

A Final Report Submission date of 31 January 2012 was originally specified for this PMR. On 19 December 2012, Pfizer requested a revised date based on a sample size of 162, and in April 2013, the Agency revised the Final Report Submission date to 31 December 2017 due to difficulties with the recruitment of pediatric patients in the study A0081180.

Pregabalin (LYRICA®) is an alpha-2-delta ligand that binds with high affinity to this auxiliary subunit of voltage-gated calcium channels in central nervous system tissues. In the United States (US), LYRICA is approved for fibromyalgia (FM), neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury, postherpetic neuralgia, and adjunctive therapy for adult patients with partial onset seizures. Lyrica is available in the US as 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules (NDA 21446), as well as a 20 mg/mL oral solution (NDA 22488).

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours. Pregabalin undergoes negligible metabolism in humans. Following oral administration of LYRICA capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is greater than or equal to 90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration,

maximum plasma concentrations (Cmax) 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 Cmax of approximately 25% to 30% and an increase in Tmax 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.

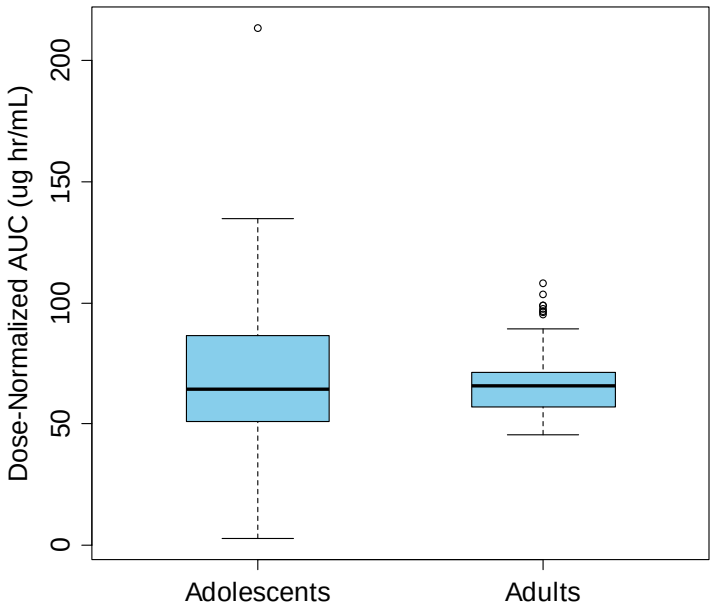
In adults, the recommended dose of LYRICA for fibromyalgia is 300 to 450 mg/day. Initiation of dosing is at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day).

Pregabalin PK has been extensively studied in healthy adults and in adult patients with partial seizures, neuropathic pain, fibromyalgia, generalized anxiety disorder, and impaired renal function. Pediatric study A0081180 "A 15-week, randomized, doubleblind, parallel-group, placebo-controlled flexible-dose safety and efficacy study of pregabalin in adolescents (12-17 years old) with fibromyalgia." In this study, two PK samples were to be collected at Week 3. A total of 82 plasma concentrations from 48 adolescent subjects were included in PK analysis. Pregabalin PK has also been evaluated in pediatric patients with partial seizures, age 3 months to 16 years (Study A0081074). Study A0081074 was an "A Placebo-Controlled, Escalating Dose, Multiple Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Pregabalin in Pediatric Patients With Partial Onset Seizures.

Analysis of blood samples collected from pediatric patients was conducted by a validated LC/MS/MS method (see attached synopsis). During the bioanalysis, the sponsor noted that 32 of the samples from study A0081074 were analyzed beyond the long-term stability data period. Population PK analysis was conducted to evaluate the effect of disease-state, linearity of PK, and dose-proprotionality across different age groups, and impact of deleting the blood samples affected by the longterm stability of samples.

A previous population PK model was derived using data from one study in 57 pediatric subjects with epilepsy down to 1 month of age and five studies in adult subjects (n=123). Pregabalin pharmacokinetics were described with a one compartment model with first order elimination, first order absorption when pregabalin was administered in the fasted state and a Weibull function when pregabalin was administered in the fed state. Creatinine clearance was an important covariate on pregabalin clearance and body weight and sex were important covariates for volume of distribution. The results of this analysis demonstrated that for the same mg dose, pregabalin exposure in pediatric patients 12 to 16 years of age is similar to adults. This finding was confirmed in A0081180 by comparing predicted pregbalain exposures to the observed concentrations in the study (see 3.2 Population PK Analysis). A comparison of exposures in the two populations is illustrated in Figure 1.

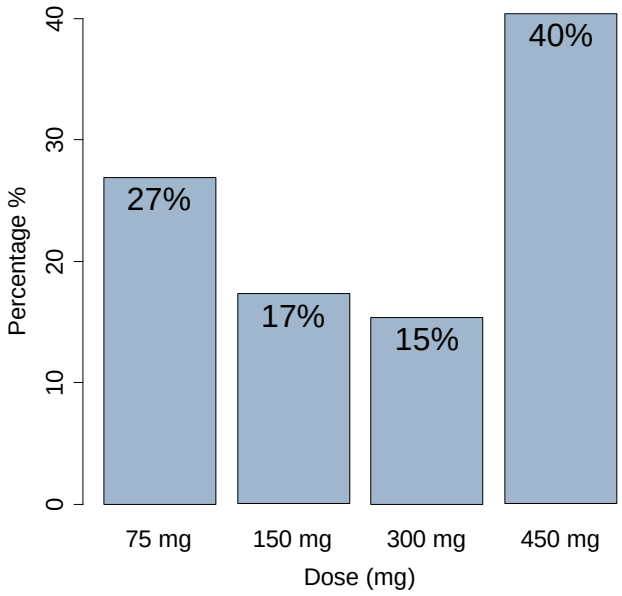
Figure 1: Comparison of Dose-Normalized AUC in Adolescents (n=48) in A0081180 to Adults (n=70)



*Adult values were derived from previous population PK analysis and included patients on doses ≥ 75 mg. AUC values were normalized to a dose of 300 mg.

Although the pharmacokinetics of pregabalin was expected to be similar in adults and adolescents, the Sponsor included doses of 75 mg/day and 150 mg/day, which are lower than the adult recommended doses of 300 mg/day and 450 mg/day, in A0081180 to "allow for smaller, low-weight adolescents who may have enrolled in the study." The results of the study suggest, however, that 44% of patients enrolled in the trial remained on doses of 75 mg/day or 150 mg/day (Figure 2). Even in patients who weighed greater than 53 kg (the median weight in the study), 34% of pediatric patients were on doses less than 300 mg/day.

Figure 2. Distribution of Optimized Doses in A0081180



The fact that patients in A0081180 were on doses lower than the adult recommended doses could have played a role in the failure of the study to demonstrate efficacy, although the potential impact cannot be quantified. It is also possible that adolescent patients are more sensitive to adverse reactions due to pregabalin. There are also other factors that may have played a role in the failure of pregabalin to demonstrate efficacy in the trial, including the limited sample size and the fact that unlike the adult efficacy trial, A0081180 was not enriched for placebo non-responders.

2.2 Summary of Labeling Recommendations

Based on the clinical pharmacology submission which comprised of PK data and the clinical safety and efficacy conclusions by the medical officer the following labeling recommendation is appropriate: "In the pediatric age group of 12 years of age and older, systemic exposure of pregabalin is similar to adults at any given dose of LYRICA."

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Pfizer Protocol No. A0081180

(b) (4) Project No. 11BAS0432

	BIOANALYTICAL STUDY REPORT: **THE DETERMINATION OF PREGABALIN IN HUMAN SODIUM HEPARIN PLASMA SAMPLES BY HPLC-MS/MS FROM PFIZER CLINICAL PROTOCOL A0081180**

Bioanalytical Laboratory	Address
(b) (4)	(b) (4)

Report Status	Final
Bioanalytical Study Start Date	26-Sep-2011
Original Report Completion Date	23-Mar-2015
Amended Report Completion Date	07-Apr-2015
Amendment to Final Report	01
Template Version and Date	Chromatographic_BAR_Version_2.0_24Aug2011

1. REPORT SUMMARY

Report Title	The Determination of Pregabalin in Human Sodium Heparin Plasma Samples by HPLC-MS/MS from Pfizer Clinical Protocol A0081180	
Pfizer Protocol Number	A0081180	
Pfizer Sponsor Location	445 Eastern Point Road, Bldg 260-2370 MS 8260-2202, Groton, CT 06340, USA	
Pfizer Principal Contact	Kimberly C. Lee	
Bioanalytical Laboratory	(b) (4)	
Bioanalytical Laboratory Project Reference	11BAS0432	
Bioanalytical Principal Investigator	(b) (4)	
Method Validation Report	(b) (4) 08BAS0048 Sponsor Reference No.: A0089002	
Method Description		
Reference Standards	Pregabalin, Lot 070289-QCS PD-403609 AKA PF-1404664, Lot P0411874 Gabapentin, Lot 101116-QCS	
Matrix	Human Plasma	
Anticoagulant	Sodium Heparin	
Method of Detection	Protein Precipitation	
Sample Aliquot Volume	50 µL	
Regression, Weighting	linear, $1/X^2$	
Calibration Range	0.0250 to 10.0 µg/mL	
Quality Control (QC) Concentrations	0.0600 µg/mL (QCL), 0.600 µg/mL (QCGM), 2.00 µg/mL (QCM), 7.50 µg/mL (QCH) and 20.0 µg/mL (QCDIL)	
Assay Performance	Precision (%CV)	Accuracy (%RE)
QC Samples (QCL, QCM, QCH and QCDIL)	≤ 4.0%	1.6% to 9.5%
Batch Performance	No. of Acceptable Runs 7	No. of Failed Runs 0
Sample Storage	Total No. of Samples	No. of Samples Analyzed
Samples Received	181	97
Storage Temperature	-20 ± 5 °C	
Storage Stability	371 days at both	-20 ± 5 °C and -70 ± 10 °C
Samples Collected and Analyzed within Stability Limits	No*	
Data Storage	Data will be stored at laboratory for a period of 15 years. Following this the sponsor will be contacted for further instructions.	
Pfizer SOP and Best Practice	(b) (4) SOP No. 02[1]	

* 32 samples were analyzed outside existing stability. These samples have been commented as "sample assayed outside existing stability" in Table 3, "Analytical Laboratory Comments" column

6. STUDY SAMPLES: SOURCE AND STORAGE

Sample Receipt			
Sample Receipt Date	Clinical Site/Central Lab	No. of Samples Received	Storage Temperature
	(b) (4)		
14-Jul-2010		2	-20 ± 5 °C
16-Sep-2011		6	-20 ± 5 °C
16-Sep-2011		33	-20 ± 5 °C
16-Sep-2011		2	-20 ± 5 °C
20-Sep-2011		56	-20 ± 5 °C
06-Mar-2012		22	-20 ± 5 °C
06-Mar-2012		14	-20 ± 5 °C
31-Aug-2012			-20 ± 5 °C
07-Mar-2013		4	-20 ± 5 °C
12-Mar-2013		16	-20 ± 5 °C

Sample Receipt			
Sample Receipt Date	Clinical Site/Central Lab	No. of Samples Received	Storage Temperature
11-Sep-2013	(b) (4)	7	-20 ± 5 °C
07-Mar-2014		2	-20 ± 5 °C
11-Mar-2014		4	-20 ± 5 °C
15-Jul-2014		5	-20 ± 5 °C
25-Nov-2014		4	-20 ± 5 °C
Total Number of Samples Received		181	
Sample Receipt Condition(s)		Frozen on dry ice	

Sample Storage Stability	
Maximum Time from Collection to Analysis	1145 Days*
Storage Stability	371 days at both -20 ± 5 °C and -70 ± 10 °C
Stability Data Reference	(b) (4) 08BAS0048 Sponsor Reference No.: A0089002
Calculated as the collection date to last analysis date of individual samples	

* 32 samples were analyzed outside existing stability. These samples have been commented as "sample assayed outside existing stability" in Table 3, "Analytical Laboratory Comments" column

7. ASSAY METHODOLOGY AND PERFORMANCE

Assay Methodology Summary	
Method Validation Report	(b) (4) Validation Report: 08BAS0048 Pfizer Validation Report ID: A0089002
Bioanalytical Method Reference	08BASM037V3
Matrix	Human Plasma
Anticoagulant	Sodium Heparin
Type of Extraction	Protein Precipitation
Method of Detection	HPLC-MS/MS
Sample Aliquot Volume	50 µL
Regression, Weighting	linear, $1/X^2$
Quantification	Peak Area Ratios
Analytical Systems Software	Analyst Version 1.4.2 (Applied Biosystems) Watson Version 7.2.0.02 (Thermo Electron Corporation)
Calibration Range	0.0250 to 10.0 µg/mL
LLOQ	0.0250 µg/mL
ULOQ	10.0 µg/mL
Dilution Factors Employed	10
Calibration Standard Distribution	Calibration standards were placed at the beginning and end of each bioanalytical batch run.
Quality Control (QC) Distribution	QC samples were distributed evenly throughout each bioanalytical batch run.
Assay Carryover Checks	A carryover blank was placed following the second ULOQ sample in each bioanalytical batch run.

Assay Selectivity
The selectivity of the method towards endogenous compounds, potential interferences and possible impurities of the internal standard was acceptable as illustrated by the chromatograms of a blank plasma sample with internal standard (zero-blank) and a blank plasma sample without internal standard (double-blank) respectively. The interference, contamination or carryover in each assay batch did not exceed 20% (>5% for internal standards) of the analyte response for the lower of two LLOQ calibration standards.

Assay Qualification Batch Run(s)
Assay qualification batch run 7 for the purposes of pre and in-study analysis checks were performed prior to the start of and on occasions during, study sample analysis. The batch run consisted of duplicate calibration lines; QC samples (n= 6) at each of 4 concentrations. The batch run was successful.

Sponsor Instructions
Do not assay placebo samples. Do not assay samples whose identity is in question.

Methodology Deviations and Bioanalytical Notes
[redacted]

SOP and Global Best Practice Deviations

After finalization of data, it was determined that 32 samples (listed below) were assayed which were not within the established 371 days of -20°C storage stability and were reported in error. These samples were commented as "sample assayed outside existing stability" in Table 3, "Analytical Laboratory Comments" column

SSID	RANDOMI-ZATION NUMBER	TREAT-MENT CODE	PFIZER/VENDOR ACCESSION	ANALYTICAL LABORATORY ACCESSION	PERIOD UNIT	PERIOD	VISIT UNIT	VISIT	TIME POST DOSE UNIT	TIME POST DOSE OR INTERVAL
10031002	5	A	A8769289-2	11BAS0432.00013	PERIOD	1	V6/WEEK	3	H	2
10031002	5	A	A8769288-2	11BAS0432.00012	PERIOD	1	V6/WEEK	3	H	0
10371022	85	A	S2674564-2	11BAS0432.00136	PERIOD	1	V6/WEEK	3	H	2
10641005	81	A	AB247816-2	11BAS0432.00152	PERIOD	1	V6/WEEK	3	H	2
10371020	76	A	S2674557-1	11BAS0432.00119	PERIOD	1	V6/WEEK	3	H	0
10371020	76	A	S2674558-2	11BAS0432.00120	PERIOD	1	V6/WEEK	3	H	2
10641006	82	A	AB247806-2	11BAS0432.00150	PERIOD	1	V6/WEEK	3	H	2
10371026	90	A	S3134220-2	11BAS0432.00139	PERIOD	1	V6/WEEK	3	H	2
10371026	90	A	S3134219-1	11BAS0432.00138	PERIOD	1	V6/WEEK	3	H	0
10371022	85	A	S2674563-1	11BAS0432.00137	PERIOD	1	V6/WEEK	3	H	0
10641005	81	A	AB247815-2	11BAS0432.00151	PERIOD	1	V6/WEEK	3	H	0
10641006	82	A	AB247805-2	11BAS0432.00149	PERIOD	1	V6/WEEK	3	H	0
10271002	4	A	A8909149-2	11BAS0432.00041	PERIOD	1	V6/WEEK	3	H	0
10271002	4	A	A8909150-2	11BAS0432.00042	PERIOD	1	V6/WEEK	3	H	2
10331007	80	A	S2848317-2	11BAS0432.00112	PERIOD	1	V6/WEEK	3	H	2
10221009	87	A	AC437437-2	11BAS0432.00155	PERIOD	1	V6/WEEK	3	H	0
10221006	69	A	AB129482-2	11BAS0432.00148	PERIOD	1	V6/WEEK	3	H	0
10071007	97	A	AD763622-2	11BAS0432.00166	PERIOD	1	V6/WEEK	3	H	2
10331007	80	A	S2848316-2	11BAS0432.00111	PERIOD	1	V6/WEEK	3	H	0
10341001	73	A	S2264821-1	11BAS0432.00113	PERIOD	1	V6/WEEK	3	H	0
10071007	97	A	AD763621-2	11BAS0432.00165	PERIOD	1	V6/WEEK	3	H	0
10071006	93	A	AD407652-2	11BAS0432.00160	PERIOD	1	V6/WEEK	3	H	0
10051005	96	A	AD514303-2	11BAS0432.00164	PERIOD	1	V6/WEEK	3	H	0
10021012	89	A	AC678571-2	11BAS0432.00157	PERIOD	1	V6/WEEK	3	H	0
10021017	98	A	AE332097-2	11BAS0432.00168	PERIOD	1	V6/WEEK	3	H	2
10021017	98	A	AE332096-2	11BAS0432.00167	PERIOD	1	V6/WEEK	3	H	0
10021012	89	A	AC678572-2	11BAS0432.00158	PERIOD		/WEEK	3	H	2
10071006	93	A	AD407653-2	11BAS0432.00161	PERIOD	1	V6/WEEK	3	H	2
10221009	87	A	AC437438-2	11BAS0432.00156	PERIOD	1	V6/WEEK	3	H	2
10071001	1	A	A8769245-4	11BAS0432.00021	PERIOD	1	V6/WEEK	3	H	2
10071001	1	A	A8769244-3	11BAS0432.00020	PERIOD	1	V6/WEEK	3	H	0
10341001	73	A	S2264822-2	11BAS0432.00114	PERIOD	1	V6/WEEK	3	H	2

9.7. **Table 7. Incurred Sample Reproducibility for Pregabalin in Human Plasma from Protocol A0081180**

SSID	Randomization Number	Treatment Code	Week	Time	Custom ID	Original Conc. µg/mL	Original Run Number	Reassay Conc. µg/mL	Reassay Run Number	Percent Difference (%)
10071007	0097	A	3	Day 21 0h	00165	1.90*	8	1.87*	10	-1.6*
10021017	0098	A	3	Day 21 0h	00167	2.96*	8	2.85*	10	-3.8*
10071001	1	A	3	Day 21 2h	00021	6.93*	1	6.77*	2	-2.3*
10331010	102	A	3	Day 21 0h	00142	1.12	8	1.10	10	-1.8
10021019	106	A	3	Day 21 2h	00172	2.02	9	1.98	10	-2.0
10021020	107	A	3	Day 21 2h	00174	0.397	9	0.392	10	-1.3
10371001	12	A	3	Day 21 0h	00053	2.54	1	2.64	2	3.9
10011003	17	A	3	Day 21 2h	00003	0.303	1	0.317	2	4.5
10451002	21	A	3	Day 21 2h	00078	2.53	1	2.44	2	-3.6
10161001	25	A	3	Day 21 0h	00024	1.45	1	1.51	2	4.1
10371006	31	A	3	Day 21 0h	00059	0.790	1	0.771	2	-2.4
10371008	33	A	3	Day 21 2h	00064	0.814	1	0.833	2	2.3
10331003	39	A	3	Day 21 0h	00048	1.29	1	1.28	2	-0.8
10281001	42	A	3	Day 21 2h	00044	1.72	1	1.63	2	-5.4
10331004	48	A	3	Day 21 0h	00050	3.21	1	3.31	2	3.1
10371012	53	A	3	Day 21 0h	00069	0.462	1	0.423	2	-8.8
10451004	57	A	3	Day 21 2h	00080	5.69	1	5.55	2	-2.5
10171001	6	A	3	Day 21 2h	00028	1.89	1	1.86	2	-1.6
10221009	87	A	3	Day 21 2h	00156	5.91*	8	5.56*	10	-6.1*
10021012	89	A	3	Day 21 0h	00157	2.31*	8	2.32*	10	0.4*
10021012	89	A	3	Day 21 2h	00158	4.51*	8	4.35*	10	-3.6*

*sample assayed outside of existing stability

Treatment Descriptions:

A: Pregabalin 75-450 mg/day

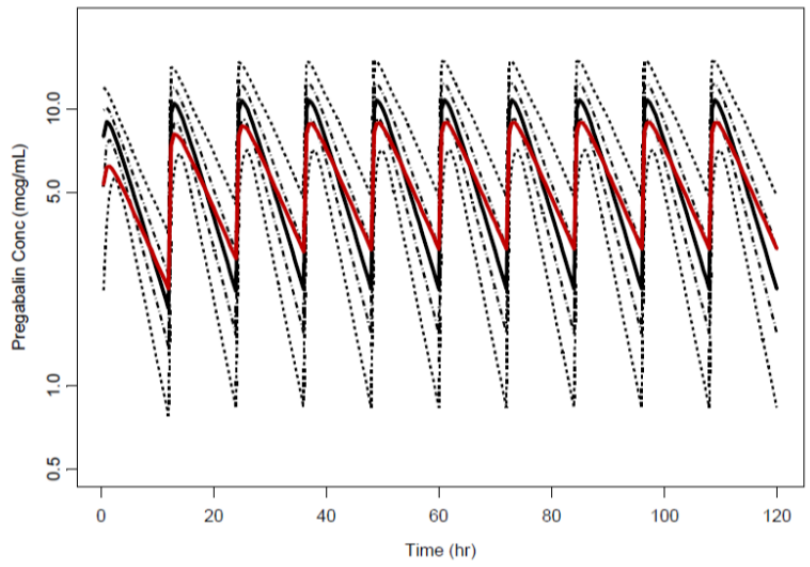
Percent Difference = [Repeat Value - Original Value]/ [Average of Repeat Value & Original Value]*100

There were 21 samples selected for ISR, all of which passed, so 100.0% of the ISR samples passed.

3.2 Population PK Analysis

The Sponsor predicted pregabalin exposures in adolescent subjects with fibromyalgia in A0081180 using a population PK model previously derived from PK data in adult and pediatric patients. The predicted concentrations were then compared to observations to evaluate concordance. The original population PK model was derived using data from one study in 57 pediatric subjects with epilepsy down to 1 month of age and five studies in adult subjects (n=123). Pregabalin pharmacokinetics were described with a one compartment model with first order elimination, first order absorption when pregabalin was administered in the fasted state and a Weibull function when pregabalin was administered in the fed state. Creatinine clearance was an important covariate on pregabalin clearance and body weight and sex were important covariates for volume of distribution. The results of this modeling exercise were used to establish dosing to be used in pediatric epilepsy efficacy trials. Predictions confirmed the expectation that adolescents and adults have similar exposure when administered the same mg dose (Figure 3).

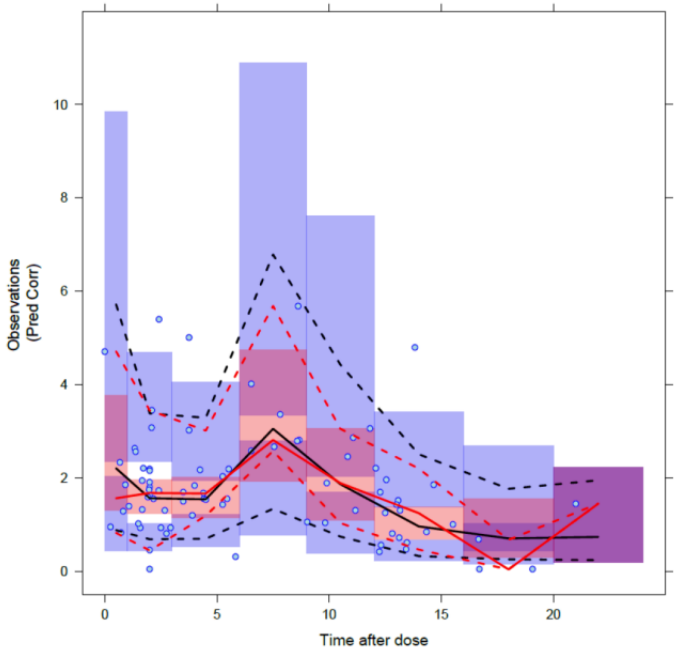
Figure 3. Predicted Pregabalin Steady State Exposure in Pediatric Subjects > 12 Years and Adults Given Dose of 600 mg/day



Source: pmar-00287, Figure 17, Page 88

This PK model was adapted to predict plasma concentrations in A0081180. Absorption in the fed state was simplified by assuming a first order absorption and the relationship between creatinine clearance and pregabalin clearance was modified to account for overweight patients. One thousand data sets were simulated and compared graphically to data from A0081180. In A0081180, two PK samples were to be collected at Week 3. A total of 82 plasma concentrations from 48 adolescent subjects were included in the analysis. Figure 4 shows the comparison between the predictions and the concentrations.

Figure 4. Prediction Corrected Observed and Simulation Pregabalin Concentrations from A0081190

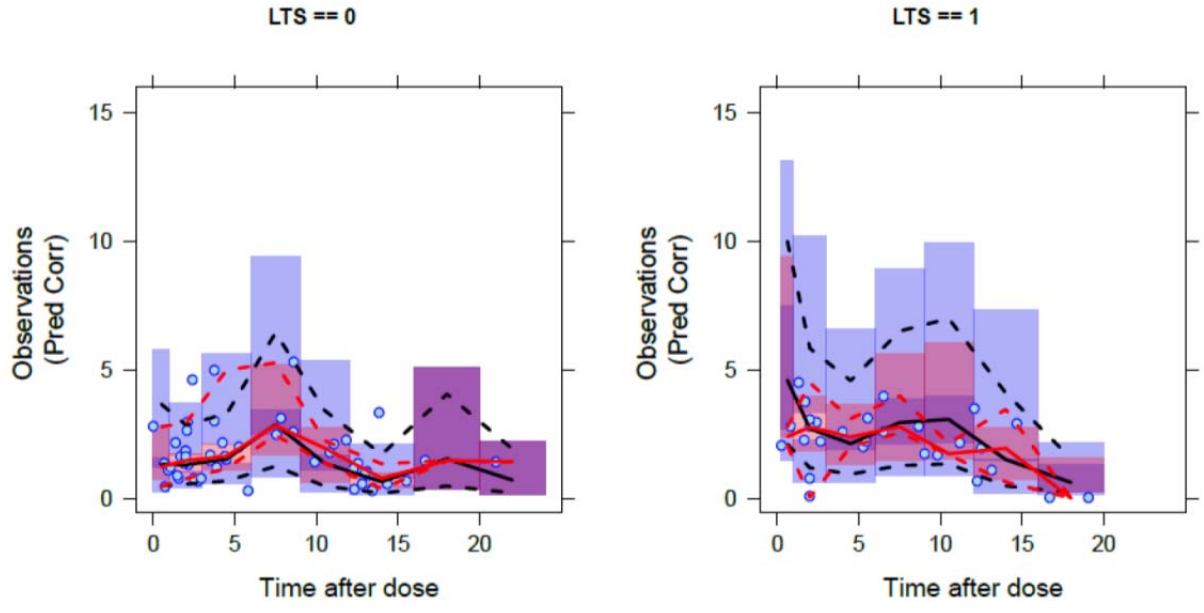


Open circles are prediction-corrected observed data. Black solid and dotted lines and red solid and dotted lines represent the median, 5th and 95th percentile of the prediction-corrected simulated and observed pregabalin concentrations, respectively. The bands around the simulated percentiles represented the 95% confidence intervals of the simulated concentrations. Bins: 1, 3, 6, 9, 12, 16, 20, 24.

Source: PMAR-EQDD-A008h-DP4-415, Figure S2, Page 6

After finalization of PK concentration data it was realized that 32 samples were assayed later than the established stability of 371 days. The simulation was repeated for samples that fell within and outside the established stability (Figure 5).

Figure 5. Prediction Corrected Observed and Simulation Pregabalin Concentrations from A0081190 (Left Panel: Samples within established stability, Right Panel: Samples outside established stability)



Open circles are prediction-corrected observed data. Black solid and dotted lines and red solid and dotted lines represent the median, 5th and 95th percentile of the prediction-corrected simulated and observed pregabalin concentrations, respectively. The bands around the simulated percentiles represented the 95% confidence intervals of the simulated concentrations. Bins: 1, 3, 6, 9, 12, 16, 20, 24 [ePharm ID: 574723]

Source: PMAR-EQDD-A008h-DP4-415, Figure 4, Page 28

Reviewer's Comments: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug and its pharmacokinetics are linear and predictable. For a given mg dose, the reviewer would expect similar exposure in adolescents and adults. The original population pharmacokinetic analysis using serial PK data in adults and children confirmed this expectation. Furthermore, the pharmacokinetic data collected from A0081180 in adolescents with fibromyalgia are generally consistent with previous data. This conclusion is independent of the observation that some of the PK samples were assayed later than the established stability. The reviewer used the Sponsor's adapted model to obtain posthoc estimates of AUC to aid in visualization of the results.

3.3 Proposed Product Label

(b) (4)

(b) (4)

[redacted]

77 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.4 Clinical Pharmacology Filing Memo.

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	021446 S32	**SDN**	1702
Applicant	Pfizer Inc.	**Submission Date**	1/29/2016
Generic Name	Pregabalin capsules	**Brand Name**	Lyrica
Drug Class	Analgesic		
Indication	Fibromyalgia		
Dosage Regimen	Titrate to effect using bid or tid regimen		
Dosage Form	Capsules	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics	Kevin Krudys, Ph.D.	Kevin Krudys, Ph.D.	
Genomics	-	-	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	4/29/2016	**74-Day Letter Date**	4/29/2016
Review Due Date	11/24/2016	**PDUFA Goal Date**	12/29/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s):

With regard to the population PK report, submit datasets used for model development and validation as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentratio and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., ba structural model, covariates models, final model, and validation model. These files should be submitted as ASCI text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☑ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		1	
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

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Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	Provided clinical overview is adequate.
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

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Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	Regular PK datasets were included. IR is being sent for population PK datasets.
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☑No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. 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?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

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/s/

SRIKANTH C NALLANI
11/22/2016

KEVIN M KRUDYS
11/22/2016

YUN XU
11/22/2016