Summary Memorandum

Date	May 22, 2019
From	Philip H. Sheridan, MD Nick Kozauer, MD Eric Bastings, MD
Subject	Summary Memorandum
NDA/BLA # Supplement#	21446 (S-036) 22488 (S-014)
Applicant	Pfizer Inc.
Date of Submission	August 27, 2018 (Major Amendment December 3, 2018)
PDUFA Goal Date	May 29, 2019
Proprietary Name / Non-Proprietary Name	Lyrica (pregabalin)
Dosage form(s) / Strength(s)	Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg; Oral solution: 20 mg/mL
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures as adjunctive therapy for patients 1 month of age and older
Recommendation on Regulatory Action	Approval

1. Background

Lyrica (pregabalin) was approved for adjunctive therapy in the treatment of partial-onset seizures in adult patients with epilepsy aged 17 years and older in June 2005. Lyrica was subsequently approved for the same indication in patients 4 years of age and older in 2018. The anticonvulsant mechanism of action for pregabalin may be related to its high affinity binding to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels).

These supplemental applications seek to extend the current indication for both the capsule and oral solution formulations of pregabalin for the adjunctive treatment of partial-onset seizures (POS) to include pediatric patients down to 1 month of age based on a randomized, double-blind, placebo-controlled pediatric clinical trial (Study A0081042). These supplemental applications, along with the supplements previously approved in 2018 (for the adjunctive treatment of partial-onset seizures (POS) to include pediatric patients down to 4 years of age), also fulfill a pediatric Written Request and Pediatric Research Equity Act (PREA) postmarketing requirements as discussed in Section 9 of this memo.

In a Type C Meeting in October 2017, the applicant asked to split this supplement into two parts, 2a and 2b. The applicant proposed to submit (as part 2a) sufficient information to fulfill their Pediatric Written Request (PWR) and PREA requirements prior to the PWR deadline of September 28, 2018, and prior to patent expiration in December 2018. The applicant proposed to submit (as part 2b) the remainder of the application necessary to allow for a new pediatric indication in patients 1 month to < 4 years of age, pending final data analysis from the conclusion of Study A0081042. The Agency agreed to this proposed plan and part 2a was submitted on August 27, 2018. At the time Part 2a application was filed, it was determined that the applicant did fulfill their PWR. On December 3, 2018, the applicant submitted Part 2b as a Major Amendment to extend the pediatric treatment indication down to 1 month of age, thus extending the PDUFA deadline by 3 months, to May 29, 2019.

2. Product Quality

The primary CMC reviewer was Dr. Richard Matsuoka.

No new product quality information was submitted.

Since this submission had no updates/changes to the approved product quality information for pregabalin (NDA 21446 and NDA 22488), this submission is adequate from a product quality perspective.

3. Nonclinical Pharmacology/Toxicology

No new data submitted or required.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by reviewers Dr. Michael Bewernitz and Dr. Dawei Li, with Dr. Kevin Krudys and Dr. Angela Men as Team Leaders.

The OCP review evaluated the acceptability of the proposed dose in patients from 1 month to < 4 years of age. Although the pharmacokinetic (PK) study (A0081074) and efficacy trial (A0081042) were open to enrollment of patients in this entire age range, the applicant was only able to enroll two patients toward the lower end of the age range (3.29 months of age in placebo arm, 3.84 months of age in the 14 mg/kg/day arm). Therefore, PK simulations were used to support dosing in this age range.

The OCP review concluded that the proposed maintenance dose (maximum of 14 mg/kg/day divided evenly and administered three times daily [TID]) is acceptable in patients 1 month to < 4 years of age based on the following considerations:

- Using different models of renal maturation, simulated exposures for the highest proposed dose level of 14 mg/kg/day TID in the subpopulation of patients age 1 to < 4 months are expected to be less than or within the range of exposures already demonstrated to be safe and effective in the older pediatric population and adults.

- Dosing begins at a low dose (3.5 mg/kg/day) and titration to the maximum dose (14 mg/kg/day) is likely to occur over a duration of several weeks. Titration based on tolerability and efficacy is expected to provide appropriate individualization for these patients. The most common adverse reaction during titration is somnolence, which is monitorable. Furthermore, titration in a patient 1-month of age can occur over a period of 6 weeks, during which time further renal maturation will proceed. The patient will be nearly 3 months of age once titration is complete, and thus nearly the age of the youngest patients in Trial A0081042.

- The total daily dose was administered TID for all patients in Trial A0081042.

The OCP review concluded that the applicant's proposed dosing regimen (as presented in Table 1 below) is acceptable.

Table 1: Proposed Lyrica Dosage Schedule for Pediatric Patients Age 1 Month to < 4 Years Old for POS

Age and Body Weight	Recommended Initial Dosage	Recommended Maximum Dosage	Frequency of Administration
Adults (17 years and older)	150 mg/day	600 mg/day	2 or 3 divided doses
Pediatric patients (b) (4) Weighing *30 kg or more*	2.5 mg/kg/day	10 mg/kg/day (not to exceed 600 mg/day)	2 or 3 divided doses

Age and Body Weight	Recommended Initial Dosage	Recommended Maximum Dosage	Frequency of Administration
Pediatric patients 4 years to younger than 17 years of age Weighing *less than 30 kg*	3.5 mg/kg/day	14 mg/kg/day	2 or 3 divided doses
Pediatric patients 1 month to younger than 4 years of age	3.5 mg/kg/day	14 mg/kg/day	3 divided doses

During titration period, increase approximately weekly based on response and tolerability.

The OCP review recommends approval and agrees with the applicant's proposed weight-based dosing for pediatric patients ages 1 month to < 4 years. I concur.

5. Clinical Microbiology

No new data submitted or required.

6. Clinical / Statistical - Efficacy

A single placebo-controlled clinical trial, Study A0081042, was submitted with the application, and intended to support the efficacy of the product for the adjunctive treatment of POS in patients 1 month to less than 4 years of age.

Controlled Study A0081042

The efficacy data from controlled trial A0081042 were reviewed by the statistical reviewers, Dr. Xiangmin Zhang, Dr. Kun Jin (Biometrics team lead), and Dr. Helen Ming Hung. Dr. Emily Freilich conducted the clinical efficacy review.

Study Design

Study A0081042 was a multi-center randomized, double-blind, placebo-controlled, parallel-group, 3-arm clinical study to evaluate the efficacy, safety, and tolerability of pregabalin in patients 1 month through < 4 years of age. Accounting for an approximately 10% discontinuation rate, approximately 123 patients were originally planned to be randomized in a 2:2:1 ratio to a placebo group, a 7 mg/kg/day pregabalin group, or a 14 mg/kg/day pregabalin group.

The study consisted of a five-day double-blind dose escalation period, a nine-day double-blind fixed dose treatment period, and a seven-day double-blind taper period. The total duration of the double-blind treatment phase was 21 days.

During the study, two 48-hour Video-Electroencephalogram (EEG) evaluations were performed: one at the baseline and the other at the end of the fixed-dose treatment period. One of the inclusion criteria of Study 1042 was that patients must have at least two partial

onset seizures, as determined by the investigator or designee during the 48-hour Video-EEG at baseline. Patients that were randomized but subsequently determined by the central reader to have less than two partial-onset seizures were allowed to continue the study. However, a central reader evaluated the Video-EEG data to determine the number of seizures for efficacy evaluation.

The primary efficacy endpoint was the change from baseline to Visit 6 in the 24-hour EEG seizure rate, as determined by the central reader. The 24-hour EEG seizure rate was defined as the number of seizures during the 48-hour EEG divided by the number of hours of Video-EEG monitoring then multiplied by 24 hours.

Statistical Methods

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized patients who took at least one dose of study drug during the double-blind treatment period, have a baseline with at least one partial onset seizure identified by Video-EEG, and a follow-up Video-EEG.

The primary endpoint of 24-hour EEG seizure rate was transformed on a logarithmic scale after adding a value of 1. Log(24-hour EEG seizure rate + 1) was analyzed using a linear model that included log(24-hour EEG seizure rate + 1) at baseline as the covariate and treatment, age at randomization (< 1 years, 1-2 years of age, > 2 years of age), and geographic region (North America + Europe + Middle East, Asia Pacific, Rest of the World) as effects.

In order to control the overall type I error, tests of the two doses were planned in the following order, each step at the two-sided significance level of 0.05:

Step 1. Test equal treatment of pregabalin 14 mg/kg/day vs placebo.
Step 2. Test equal treatment of pregabalin 7 mg/kg/day vs placebo.

A blinded sample size re-estimation using the method described in Keiser and Friede (2011) [1] was planned to be conducted when approximately two thirds of the patients had completed the study.

Results

Demographic characteristics of the enrolled patients indicated that the treatment groups appeared similar in terms of age, sex, and race. The average age of the enrolled patients was 28.2 months (standard deviation (SD) = 12.6 months). Overall, there were more male patients in the study (59%). The majority of the enrolled patients were white (68.6%).

The total number of patients randomized were 175 and the total number of patients in the mITT efficacy analysis population was 140.

Table 2, reproduced from the Biometrics review, summarizes the results of the primary efficacy analysis:

Table 2: Primary Efficacy Results from Study A0081042 (mITT population)

Visit		Pregabalin 7 mg/kg/day (N=59)	Pregabalin 14 mg/kg/day (N=28)	Placebo (N=53)
Baseline	n	59	28	53
	Min	0.5	0.3	0.3
	Median	1.73	1.86	1.37
	Max	5.5	3.8	4.0
	Mean	2.03	1.86	1.66
	95% CI of Mean	(1.73, 2.33)	(1.49, 2.23)	(1.40, 1.91)
	SD	1.157	0.945	0.920
DB Phase	n	59	28	53
	Min	0.0	0.0	0.0
	Median	1.57	0.87	1.19
	Max	5.7	3.5	4.5
	Mean	1.81	1.10	1.36
	95% CI of Mean	(1.49, 2.12)	(0.69, 1.51)	(1.03, 1.69)
	SD	1.219	1.065	1.193
	LS Mean	1.69	1.15	1.58
	95% CI of LS Mean	(1.46, 1.92)	(0.83, 1.47)	(1.32, 1.83)
	Standard error	0.115	0.163	0.129
	Versus Placebo (log)			
	LS Mean Difference	0.11	-0.43	
	95% CI of LS Mean Difference	(-0.19, 0.42)	(-0.80, -0.06)	
	Standard error	0.153	0.185	
	p-value	0.4606	0.0223	

Source: Table 13 in the clinical study report body

As depicted in the table, the Biometrics review confirms that patients treated with pregabalin 14 mg/kg/day had, on average, a 43.9% greater reduction in the rate of partial-onset seizures than patients treated with placebo (p=0.02).

For the key secondary endpoint, pediatric patients treated with pregabalin 14 mg/kg/day showed a numerical (but not statistically significant) improvement in responder rates (≥50% reduction in partial-onset seizure frequency) compared with placebo (53.6% versus 41.5%).

Patients treated with pregabalin 7 mg/kg/day did not show improvement relative to placebo for either endpoint.

The Biometrics review observes that the efficacy results appeared to be disproportionally affected by the results in three foreign study centers. The biometrics review further notes that after removing data from any one of the three centers, the pregabalin-placebo comparisons no longer reached statistical significance. However, the review finds that removing data from any one of the three centers would reassuringly still provide results favoring the pregabalin 14 mg/kg/day group. For example, the overall percentage of seizure rate reduction relative to placebo was 43.9%. This percentage would change to 41%, 40%, or 36.5%, if Center 1069, Center 1084, or Center 1209, respectively, was removed. A data audit of one of these sites (Dr. Yulia Karakulova, M.D., Ph.D.) by the

Office of Scientific Investigation did not identify any concerns that would impact the interpretability of the results from that site.

The statistical reviewers, Dr. Xiangmin Zhang and Dr. Kun Jin, concluded, "Based on the statistical evidence from Study A0081042, pregabalin appears effective as adjunctive therapy for children 1 month through < 4 years of age with partial onset seizures." Dr. Freilich similarly concludes that the efficacy data provided in the application support approval.

I agree with the statistical and clinical reviewers' conclusion. Additionally, a single positive efficacy study is sufficient to support approval for children 1 month through < 4 years of age as the already established efficacy of pregabalin for the adjunctive treatment of POS in patients 4 years of age and older provides confirmatory evidence.

7. Safety

The safety data in this submission were reviewed by Dr. Emily Freilich, clinical reviewer.

The primary sources of safety data were the following:

- Study A0081042: A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and short-term safety of pregabalin as adjunctive therapy in children 1 month to <4 years of age with POS.

- Study A0081075: A 12-month, open-label extension study evaluating the safety and tolerability of flexible doses of pregabalin in pediatric patients with POS who had previously participated in pharmacokinetic study A0081074.

- Study A0081106: A 12-month, open-label extension study evaluating the safety and tolerability of pregabalin as adjunctive therapy in pediatric patients 1 month to 16 years of age with POS and pediatric and adult patients 5 to 65 years of age with primarily generalized tonic-clonic (PGTC) seizures.

Dr. Freilich's review comments that, because there was a single placebo-controlled study (Study 1042) and two open-label extension studies (Studies 1075 and 1106) which lacked comparators, the data from all 3 studies were not pooled for the majority of the analyses. The three safety populations (including patients age 3 months to < 4 years) analyzed were controlled data from Study 1042 (n = 175), controlled/uncontrolled data from the safety pool of all three studies 1042, 1075, and 1106 (n = 182), and safety data from Phase 1 PK study 1074 (n = 26).

7.1. Deaths

There were no deaths in Study 1042.

Four patients died during the long-term extension studies (Studies 1075 and 1106). None of the deaths were assessed by the investigators, applicant, or Dr. Freilich as causally related to pregabalin.

7.2. Nonfatal Serious Adverse Events

There were 5 serious adverse events (SAEs) during Study 1042, as noted in Table 3 below from Dr. Frielich's review, with only one of these events in a patient on pregabalin (a case of pneumonia in a patient on 14 mg/kg/day).

Table 3: Treatment-Emergent Adverse Events - Safety Analysis Set

	Pregabalin 7 mg/kg N = 71 n (%)	Pregabalin 14 mg/kg N = 34 n (%)	Placebo N = 70 n (%)	Total N = 175 n (%)
TEAEs	32 (45.1)	17 (50.0)	38 (54.3)	87 (49.7)
SAEs	0	1 (2.9)	4 (5.7)	5 (2.9)
Severe AEs	0	0	0	0
Discontinued due to AEs	0	0	1 (1.4)	1 (0.6)

Source: Adapted from Study 1042 CSR Table 17, clinical reviewer- verified

None of the SAEs led to discontinuation from the study. The SAEs are briefly described below, including one patient who was randomized to pregabalin 14 mg/kg/day and 4 patients who were randomized to placebo.

In the long-term extension studies, there were 33 patients who had SAEs. The only SAEs that occurred in more than one patient were pneumonia, seizure, asthma, and status epilepticus. Three of these patients, with SAEs of status epilepticus, seizures, and thrombocytopenia, were permanently discontinued from the studies. The case of thrombocytopenia was subsequently determined to be a laboratory error.

The incidence and character of the SAEs did not appear to be substantially different from what has been previously reported in the adult clinical trials. No new safety signals were identified.

7.3. Dropouts and Discontinuations

No patients in either pregabalin group discontinued treatment due to TEAEs. There was one patient in the placebo group who discontinued treatment after a TEAE of vomiting.

In the long-term open-label extensions, three patients discontinued due to SAEs.

No new safety signals were identified by the applicant or by Dr. Freilich.

7.4. Common Adverse Events

Table 4 below lists all dose-related adverse reactions occurring in at least 2% of all pregabalin-treated patients. Dose-relatedness was defined as an incidence of the adverse event in the 14 mg/kg/day group that was at least 2% greater than the rate in both the placebo and 7 mg/kg/day groups. In this study, 105 patients received pregabalin and 70 patients received placebo for up to 14 days.

Table 4. Dose-related Adverse Reaction Incidence in a Controlled Trial in Adjunctive Therapy for Partial-Onset Seizures in Patients 1 Month to Less Than 4 Years of Age

Body System Preferred Term	**7 mg/kg/day [N=71] %**	**14 mg/kg/day [N=34] %**	**All PGB [N=105] %**	**Placebo [N=70] %**
Nervous system disorders				
Somnolence*	13	21	15	9
Infections and infestations				
Pneumonia	1	9	4	0
Viral infection	3	6	4	3

Abbreviations: N=number of patients; PGB=pregabalin.
* includes related terms including lethargy, sluggishness, and hypersomnia.

The types of TEAEs were similar to those reported in the adult clinical trials. Although incidence rates cannot be directly compared between the short-term controlled adult studies and the long-term open-label pediatric studies, there did not appear to be a substantial difference in rates of reported events to raise a concern for a new or unique safety signal in the pediatric population.

7.5. Adverse Events of Interest

The following adverse events were prospectively identified to be of interest for pregabalin and the pediatric patient population.

- Dizziness
- Somnolence
- Edema
- Weight gain
- Vision-related events
- Ataxia
- Tremor

- Cognitive/neuropsychiatric events including behavioral effects (behavior/aggression, concentration/personality changes, or hyperkinesia)
- Euphoric effects
- Suicidal ideation and behavior

Dr. Freilich did not identify and new safety signals with respect to the preceding list of AEs.

7.6. Laboratory Findings/Vitals/ECG

No clinically meaningful changes in laboratory assessments, vital signs, weight, or ECGs were identified by Dr. Freilich.

7.7. Safety by Age Group

Dr. Freilich did not identify any significant differences in the incidence or quality of TEAEs across the age groups.

With regard to age representation in the pivotal controlled trial (Study 1042), Dr. Freilich discussed in her review that there are no patients under 4 months of age who received pregabalin during the double-blind treatment phase. There were only a few patients under 1 year of age in all treatment arms of the study. The applicant is proposing an indication down to 1 month of age. Although there is decreased renal clearance in patients 1 to 3 months of age, the clinical pharmacology reviewer has addressed the safety of the starting dose based on the PK simulations provided by the applicant for this age group (discussed above). Furthermore, from a clinical perspective, there are no safety concerns that would preclude using the drug in patients age 1 month to less than 4 months of age, given the conservative approach in labeling to dosing (starting at a low dose and titrating up to a maximum dose based on tolerability and clinical response). The most common adverse event is dose-dependent somnolence, which would be able to be monitored for, and, given the dose titration schedule, even the youngest patients at 1 month of age would be closer to 3 months of age by the time they reached the maximum dose. The conservative dosing regimen in labeling also accommodates interpatient variability. Therefore, there are no safety concerns to expanding the indication down to the youngest age at which POS can be diagnosed, i.e., 1 month.

7.8. Postmarketing Experience

Based on the available postmarketing reports from limited use in pediatric patients less than 4 years of age, there were no new safety signals identified.

7.9 Overall Safety Conclusion by the Clinical Reviewer

I agree with Dr. Freilich's conclusion that there are no new safety concerns identified with the use of pregabalin in the pediatric population and that the safety data from the current application support an approval for the adjunctive treatment of POS in patients 1 month to less than 4 years of age.

8. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile of pregabalin is acceptable for the proposed indication.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee (PeRC) on May 1, 2019.

The January 4, 2010, approval letter for Lyrica Oral Solution (NDA 22488) includes the following deferred PREA postmarketing requirements:

1576-2 Deferred pediatric study under PREA, a randomized, double-blind, placebo-controlled study to evaluate the efficacy, pharmacokinetics, and safety of pregabalin in pediatric patients with partial onset seizures ages 1 month through 3 years of age, inclusive.

Upon review of the current application, the above requirement has been fulfilled.

The June 10, 2005, approval letter for Lyrica capsules (NDA 21724) and the January 4, 2010, approval letter for Lyrica Oral Solution (NDA 22488) include the following deferred PREA postmarketing requirements:

1359-4: Deferred pediatric study under PREA for the treatment of partial onset seizures in pediatric patients ages 1 month [44 weeks gestational age] to 16 years.

1576-4: Deferred pediatric study under PREA, a 12-month open label extension study to evaluate the safety of pregabalin in pediatric patients with partial onset seizures ages 1 month through 16 years, inclusive.

Upon review of the current application (combined with the previous supplemental applications approved in 2018 for pediatric 4 to 16 years of age), these deferred PREA postmarketing requirements for studies conducted in the age group of 4 to 16 years have been fulfilled.

Pediatric Written Request

A pediatric Written Request (WR) was originally issued on June 8, 2005, and amended on October 17, 2006, July 30, 2010, September 26, 2013, and March 23, 2017. These supplemental applications (combined with the previous supplemental applications approved in 2018 for pediatric 4 to 16 years of age) fulfill the requirements of this amended WR for studies conducted in the age group of 1 month to 16 years.

10. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

11. Postmarketing

The approval letter will reiterate that there is a postmarketing requirement listed in the December 30, 2004 (NDA 21446), June 10, 2005 (NDA 21724), and January 4, 2010 (NDA 22488), approval letters that remains open:

1118-1 & 1359-1: Complete an adequate and well-controlled clinical study or studies to better assess the ophthalmologic effects of pregabalin.

12. Recommendations/Risk Benefit Assessment

The applicant has provided substantial evidence of effectiveness for the adjunctive use of pregabalin capsules and oral suspension in pediatric patients aged 1 month to less than 4 years with POS, based on a randomized, double-blind, placebo-controlled pediatric clinical trial (Study A0081042).

Safety for the pediatric population was analyzed in a total of 182 patients 3 months to 3 years of age with POS that were treated with pregabalin in controlled Study A0081042 or open-label extension Studies A0081075 and A0081106. There are no new safety concerns identified with the use of pregabalin in the proposed pediatric population. There are no outstanding unresolved issues.

The risk-benefit profile of pregabalin for the proposed indication in the proposed population is acceptable and supports the approval of the application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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05/22/2019 05:23:19 PM

NICHOLAS A KOZAUER
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I concur.