# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | NDA 021446/SUPPL-36 (sequence 0553)<br>NDA 022488/SUPPL-14 (sequence 0084) |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA021446\0553<br>\\CDSESUB1\evsprod\NDA022488\0084 |
| **Submission Date** | 08/27/2018 |
| **Submission Type** | Efficacy Supplement |
| **Brand Name** | Lyrica® |
| **Generic Name** | Pregabalin |
| **Dosage Form and Strength** | Capsules: 25, 50, 75, 100, 150, 200, 225, 300 mg<br>Oral Solution: 20 mg/mL |
| **Routes of Administration** | Oral |
| **Proposed Indication** | Adjunctive therapy for the treatment of partial onset seizures in patients 1 month to less than 4 years of age |
| **Relevant Approved Indication** | Adjunctive therapy for the treatment of partial onset seizures in patients 4 years of age and older |
| **Applicant** | Pfizer Inc. (PF PRISM CV) |
| **Associated IND** | 49393 |
| **OCP Review Team** | Dawei Li, Ph.D.<br>Michael Bewernitz, Ph.D.<br>Kevin Krudys, Ph.D.<br>Angela Men, M.D., Ph.D. |

# 1 EXECUTIVE SUMMARY

Lyrica (pregabalin) is currently approved in the U.S. for the treatment of partial-onset seizures (POS) as an adjunctive therapy in patients 4 years of age and older.

An efficacy supplement 21446/36 & 22488/14 was submitted to pursue an indication for Lyrica (capsules and oral solution) for the adjunctive treatment of POS in patients 1 month to less than 4 years of age. The current submission includes the results of a double-blind, placebo-controlled, parallel-group trial (A0081042) in this population. A statistically significant reduction in 24-hour seizure frequency during the double-blind period compared with placebo occurred in the 14 mg/kg/day arm (44% reduction) but not in the 7 mg/kg/day arm.

The main objective of this review was to evaluate the acceptability of the proposed dose in patients from 1 month to < 4 months of age. Although the pharmacokinetic (PK) study (A0081074) and efficacy trial (A0081042) were open to enrollment of subjects in this age range, the Applicant was only able to enroll two subjects at the upper end of the age range (3.29 months in placebo arm, 3.84 months in the 14 mg/kg/day arm). Therefore, PK simulations were used to support dosing in this age range.

The review team found the proposed maintenance dose (maximum of 14 mg/kg/day divided evenly and administered three times daily [TID]) to be acceptable in subjects 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 subjects 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 (please refer to the clinical review). Furthermore, titration in a subject 1-month of age can occur over a period of 6 weeks during which renal maturation will proceed. The subject 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 subjects in Trial A0081042.

The Applicant's proposed dosing regimen, which OCP finds acceptable, is presented in Table 1 below.

**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 |
| 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.*

## 2 RECOMMENDATIONS

The Office of Clinical Pharmacology has assessed NDA 021,446/Suppl-36 and NDA 022,488/SUPPL-14, for Lyrica (pregabalin). The submission is acceptable from the perspective of the Office of Clinical Pharmacology. We recommend approval provided an agreement is reached between the Agency and the Applicant regarding labeling language.

## 3 BACKGROUND

Pregabalin is currently approved as adjunctive therapy for partial onset seizures (POS) in patients age 4 years and older. Though the mechanism of action is unknown, Lyrica is thought to act at alpha2-delta site (an auxillary subunit of voltage-gated calcium channels). The safety and effectiveness of Lyrica as adjunctive treatment for partial onset seizures in pediatric patients 4 to less than 17 years of age was established in a double-blind, placebo-controlled trial. The currently-approved dosing regimen for adjunctive therapy of POS in patients 4 years of age and older is found in Table 2.

**Table 2: Currently Approved Lyrica Dosage for Patients 4 Years and Older for Adjunctive Therapy for POS**

| Age and Body Weight | Recommended Initial Dosage (administer in two or three divided doses) | Recommended Maximum Dosage (administer in two or three divided doses) |
|---|---|---|
| Adults (17 years and older) | 150 mg/day | 600 mg/day |
| Pediatric patients weighing ≥ 30 kg | 2.5 mg/kg/day | 10 mg/kg/day (not to exceed 600 mg/day) |
| Pediatric patients weighing 11 to < 30 kg | 3.5 mg/kg/day | 14 mg/kg/day |

# 4 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

**Summary of Pediatric Development**: The Applicant conducted a pediatric PK study (A0081074) in pediatric patients with POS age 1 month to 16 years. Next, the Phase 3 efficacy trial A0081041 in patients age 4 to 16 years was conducted. Study A0081074 and Trial A0081041 were submitted in Supplement 35 which resulted in approval of a POS indication in pediatric patients age ≥ 4 years. The Applicant subsequently conducted Phase 3 efficacy trial A0081042 to assess efficacy in patients age 1 month to < 4 years. Trial A0081042 was submitted in the current submission, Supplement 36, to support approval of a POS indication in patients age 1 month to < 4 years.

**A0081042 (Phase 3):** Phase 3 trial A0081042 is a double-blind, placebo-controlled, parallel-group trial to assess efficacy in n=175 patients with POS age 1 month through < 4 years with partial onset seizures.

[*Reviewer comment: The Applicant attempted to enroll subjects as young as 1 month of age. However, the youngest patient recruited was 3.84 months of age.*]

Patients were randomized in a 2:1:2 ratio to receive 3 weeks of treatment at low-dose (7 mg/kg/day) Lyrica, high-dose (14 mg/kg/day) Lyrica, or placebo. Subjects randomized to pregabalin 7 mg/kg/day started treatment with pregabalin 3.5 mg/kg/day for 5 days and then received 7 mg/kg/day. Subjects randomized to pregabalin 14 mg/kg/day received 3.5 mg/kg/day for 2 days, 7 mg/kg/day for 3 days, and then 14 mg/kg/day. In anticipation of potentially lower pregabalin clearance in younger subjects, the Applicant planned to reduce pregabalin doses from 3.5 mg/kg/day to 3 mg/kg/day, 7 mg/kg/day to 6 mg/kg/day or 14 mg/kg/day to 12 mg/kg/day in subjects 1 to 3 months of age.

Following the 5-day titration, subjects received the fixed dose for 9 days and underwent tapering down over a 7-day period. The full 21 days of treatment were double-blind. The total daily dose was split evenly and administered TID.

[*Reviewer comment: Only one patient in Trial A0081042, Subject* (b) (6) *was less than 4 months of age at enrollment (3.84 months) and also randomized to receive Lyrica. However, the Applicant did not reduce the dose level during titration (3.5 mg/kg/day followed by 7 mg/kg/day), nor maintenance (14 mg/kg/day), nor tapering (7 mg/kg/day followed by 3.5 mg/kg/day). Subject* (b) (6)*, was 3.28 months of age at enrollment but was randomized to placebo. Thus, trial A0081042 did not provide any data regarding the proposed reduced Lyrica dose levels in patients age 1 month to 3 months.*]

Sparse PK were collected (two samples at Visit 4 [Day 6; beginning of fixed treatment phase], one sample at Visit 6 [Day 15; beginning of the taper phase]). The primary endpoint of this study is log-transformed double-blind 24-hour seizure rate for all POS collected at Visit 6 (over 48-hour period).

The efficacy analyses indicate that 14 mg/kg/day was statistically superior to placebo (44% reduction in mean seizure rate relative to placebo; p=0.0223) and 7 mg/kg/day was not (15% mean increase in mean seizure rate relative to placebo; p=0.4606). Please refer to the review written by the Biostatistics reviewer for details.

[*Reviewer comment: The results of Trial A0081042 appear to support effectiveness of the 14 mg/kg/day dose level, administered TID, in pediatric patients age 3 months (the youngest patient enrolled in the study) to < 4 years. As the Applicant is proposing labeling down to 1 month of age, support for this age group comes in the form of providing doses that match exposure to older pediatric patients and adults (see section 5).*]

Other relevant studies include a Phase 1 PK study in pediatric POS patients (A0081074; age 1 month to 16 years) and a Phase 3 efficacy trial in pediatric POS patients (A0081041; age 4 to 16 years). Studies A0081047 and A0081041 were previously-reviewed in a prior supplement (for details, please refer to the clinical pharmacology review of NDA 0214446, Supplement 35, archived on 05/02/2018). An overview of these studies is provided below.

**A0081074 (Phase 1; Previously-Reviewed)**: Phase 1 study A0081074 is a placebo-controlled, single ascending dose, multiple-ascending dose study in n=65 patients with POS age 1 months to 16 years.

[*Reviewer comment: The Applicant intended to recruit subjects down one month of age in study A0081074. However, the youngest patient recruited is listed as 0.3 years, approximately 3.6 months.*]

Patients were randomized to receive placebo, 2.5, 5, 10, or 15 mg/kg/day (max 150, 300, 600, or 900 mg/day, respectively) administered BID for 7.5 days (7 days BID administration and a single administration on the morning of Day 8). Patients in the placebo arm received their first and only Lyrica administration on Day 8 after 7 days of receiving placebo. With respect to the Day 8 administration, PK was sampled pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose.

**A0081041 (Phase 3; Previously-Reviewed)**: Phase 3 trial A0081041 is a double-blind, placebo-controlled, parallel trial to assess efficacy in n=295 patients with POS age 4 to 16 years. Patients were randomized to 12 weeks of either placebo, low-dose Lyrica, or high-dose Lyrica. In the low dose Lyrica arm, Lyrica was administered 3.5 mg/kg/day to patients < 30 kg and 2.5 mg/kg/day for patients ≥ 30 kg, maximum 150 mg/day, without titration/escalation. In the high dose Lyrica arm, Lyrica was administered 14 mg/kg/day for patients < 30 kg and 10 mg/kg/day for patients ≥ 30 kg, maximum 600 mg/day, with a 2-week escalation period. The starting dose in the high dose Lyrica arm was the same dose as was applied in the low-dose arm. The total daily dose was split evenly and administered BID. Sparse PK were collected (1 sample at Visit 7, two samples at Visit 9). The primary endpoint of this study was the evaluation of the frequency of partial onset seizures standardized to a 28-day duration.

## 5 RESULTS OF APPLICANT'S POPULATION PK ANALYSES

The Applicant conducted population PK (PPK) modeling and simulation to inform dose selection in pediatric patients age 1 month to 4 years of age. The Applicant started with a previously-developed PPK model built with data from adults and pediatric patients age ≥ 3 months (from report PMAR 538; sequence 0408) and updated the parameter estimates after pooling the dataset with PK data from pediatric patients age 3 months to < 4 years in pediatric trial A0081042 (from report PMAR 689; sequence 0553). All PPK modeling was conducted in NONMEM version 7.3.

Previous Adult and Pediatric Population PK Model: The previous PPK model (sequence 0408, PMAR-EQDD-A008s-sNDA-538.pdf) was built using PK data from adults and pediatric patients down to 3 months of age. This model was previously reviewed by OCP and found to be acceptable (please refer to the clinical pharmacology review of NDA 021446, SUPPL-35, archived on 05/02/2018 for details). PK data used in the modeling procedure came from study A0081074 (n=60 subjects, 419 observations) and trial A0081041 (n=187 subjects, 505 observations).

The model utilized a one-compartment distribution model, first-order oral absorption with lag time, first-order elimination, and was parameterized in terms CL/F (apparent clearance), V/F (apparent volume of distribution), three $k_a$ (first order absorption rate constant) terms (one for fasted, fed, and unknown food states), and two $T_{lag}$ terms (for fasted and unknown food state, estimated from adult PK data). Covariates for CL/F include body weight, creatinine clearance, and sex. Covariates for apparent volume of distribution include body weight and sex. Weight was normalized to 70 kg and related to CL/F and V/F using power models. Creatinine clearance was normalized by body-surface area (BSA) and related to CL/F using a so-called "hockey stick model". In the "hockey stick model", CL/F is proportional to creatinine clearance up to a breakpoint creatinine clearance value. For creatinine clearance values at and above the breakpoint, CL/F remains constant.

Between-subject variability (BSV) was estimated for CL/F, V/F, and $k_a$ for the combined adult and pediatric populations except for a separate $k_{a,fed}$ BSV term (for which only adult data are available).

Current Adult and Pediatric Population PK Model: The Applicant refined the previously-developed model (from report PMAR 538) by pooling PK data from Trial A0081042 (n=103 subjects, 304 observations) with the two studies used in the previously-developed model (study A0081074 and trial A0081041). The only new parameter is the addition of an additive residual error term specific to Trial A0081042. The current PPK model is described in report pmar-eqdd-a008s-snda-689.pdf in sequence 0553.

The final model parameter estimates for the previous PPK model and current PPK model are presented for comparison in Table 3.

**Table 3: Comparison of PK Parameter Estimates From Previous PPK Model (from Report PMAR-538) Versus Current PPK Model (from Report PMAR-689)**

| Model<br>Parameter | Previous PPK Model (PMAR-538*) | Current PPK Model (PMAR 689**) | % change |
|---|---|---|---|
| CL/F [L/h] ($\Theta_1$) | 4.96 | 4.94 | -0.4% |
| BWT on CL/F ($\Theta_{10}$) | 0.522 | 0.542 | 3.8% |
| Sex on CL/F ($\Theta_{13}$) | 0.915 | 0.923 | 0.9% |
| CLcr breakpoint [mL/min/1.73 $m^2$] ($\Theta_5$) | 96.4 | 95.8 | -0.6% |
| V/F [L] ($\Theta_2$) | 39.8 | 39.7 | -0.3% |
| Sex on V/F ($\Theta_7$) | 0.832 | 0.829 | -0.4% |
| BWT on V/F ($\Theta_8$) | 0.704 | 0.705 | 0.1% |
| $k_a$ Fasted [$h^{-1}$] ($\Theta_3$) | 10.0 | 10.1 | 1.0% |
| Food: Fed [$h^{-1}$] ($\Theta_6$) | 0.708 | 0.99 | 39.8% |
| Food: unknown [$h^{-1}$] ($\Theta_9$) | 1.22 | 1.17 | -4.1% |
| $T_{lag}$ [h] ($\Theta_4$) | 0.318 | 0.318 | 0% |
| Food: Fed ($\Theta_{20}$) | 0.427 | 0.427 | 0% |
| **Interindividual Variability [%]** | | | |
| CL/F ($\omega_1$) | 20.2 | 21 | 4.0% |
| V/F ($\omega_2$) | 12.8 | 12.4 | -3.1% |
| $k_a$ ($\omega_3$) | 117 | 121 | 3.4% |
| $k_{a,Fed}$ ($\omega_4$) | 57.9 | 82.9 | 43.2% |
| **Proportional Error [%]** | | | |
| Phase 1 Adults ($\sigma_1$) | 16.6 | 16.6 | 0% |
| Phase 3 Adults ($\sigma_2$) | 28.9 | 28.7 | -0.7% |
| Phase 1 Pediatrics (A0081074) ($\sigma_7$) | 29.8 | 29.7 | -0.3% |
| Phase 3 Pediatrics (A0081041 and A0081042) ($\sigma_5$) | 35 | 37.1 | 6.0% |
| **Additive Error [µg/mL]** | | | |
| Phase 1 Adults ($\sigma_3$) | 0.0214 | 0.0214 | 0% |
| Phase 3 Adults ($\sigma_4$) | 0.0466 | 0.0474 | 1.7% |
| Phase 3 Pediatrics (A0081041) ($\sigma_6$) | 0.682 | 0.665 | -2.5% |
| Phase 3 Pediatrics (A0081042) ($\sigma_8$) | --- | 0.033 | --- |

** Adult patients and pediatric patients age ≥ 3 months, PMAR-538 (A0081074, A0081041*

***Adult patients and pediatric patients age ≥ 3 months, PMAR-689 (A0081074, A0081041, A0081042)*

*Source: sequence 0553, pmar-eqdd-a008s-snda-689.pdf, page 48-49 of 176*

[*Reviewer comment: The current population PK model retained the same structural parameters, random effects parameters, and covariates as the previous population PK model. The only new parameter in the current model is an additive residual error term for the additional trial included in the PK data pool, Trial A0081042, which is acceptable.*

*Most model parameter estimates are comparable between the two models such that the absolute value of parameter change is ≤ 6%. The largest change in parameter estimate occurred for "Food: Fed [$h^{-1}$] ($\Theta_6$)," fractional change in $k_a$ for subjects in a fed status (increase by 39.8%) and "$k_{a,Fed}$ ($\omega_4$)" (increase by 43.2%). However, as $k_a$ is not expected to affect calculation of $C_{minss}$ or $C_{avgss}$, and Lyrica may be taken with or without meals, the food effect changes are not expected to have clinical relevance. Overall, the current PPK model described in report (PMAR-689) is acceptable.*]

Applicant's PK Simulations to Inform Pediatric Maintenance Dose Selection: Applicant conducted PK simulations in virtual adult patients and virtual pediatric patients to support pediatric dose selection in patients age 1 month to < 4 years. Individual PK parameter estimates were simulated in NONMEM version 7.3. Individual PK parameter estimates were used to compute individual exposures in R.

*Maintenance Dose Target*: Applicant utilized the highest approved maintenance dose level in adults of 600 mg/day as the target for selecting the highest pediatric maintenance dose in patients age 1 month to 4 years. Simulations were conducted with TID administration in pediatric patients age 1 month to 4 years and BID as well as TID in adults.

*Simulation Methodology*: The current PPK model was used to conduct PPK simulations in a fasted state. This PPK model retains the original "hockey stick" model to account for the effect of to creatinine clearance on pregabalin apparent clearance. However, for the PK simulations the Applicant also utilized an alternate method to account for the effect of renal function on pregabalin apparent clearance. The two approaches to account for the effect of renal function on pregabalin clearance in pediatric patients are described below.

- Renal Function Simulation Approach 1: This approach is identical to the population PK model. The creatinine clearance was estimated using the modified Schwartz equation using k=0.55 for patients age ≥ 1 year to age < 4 years as well as k=0.45 for subjects age < 1 year. The creatinine clearance values were normalized to body surface area to create body-surface-area-normalized creatinine clearance (NBCCL). The NBCCL values were applied into the "hockey stick model" used to compute the proportional effect of NBCCL on pregabalin CL/F.

- Renal Function Simulation Approach 2: In approach 2, the NBCCL for individual patients is not used. In this approach the Applicant modified the PPK model such that that the CL/F is fractionally reduced according to creatinine clearance as predicted by *age*

rather than the *NBCCL*. The sigmoid $E_{max}$ term used to represent renal maturation is a component of the full GFR equation in Rhodin et al[1]. The sigmoid $E_{max}$ model is parameterized in terms of the pediatric patient's post-menstrual age (age period from gestation time plus the time after birth, in weeks), a Hill coefficient of 3.4, and a renal maturation half-time ($TM_{50}$) of 47.7 weeks. Full renal maturation occurs near 2 years of age using this model.

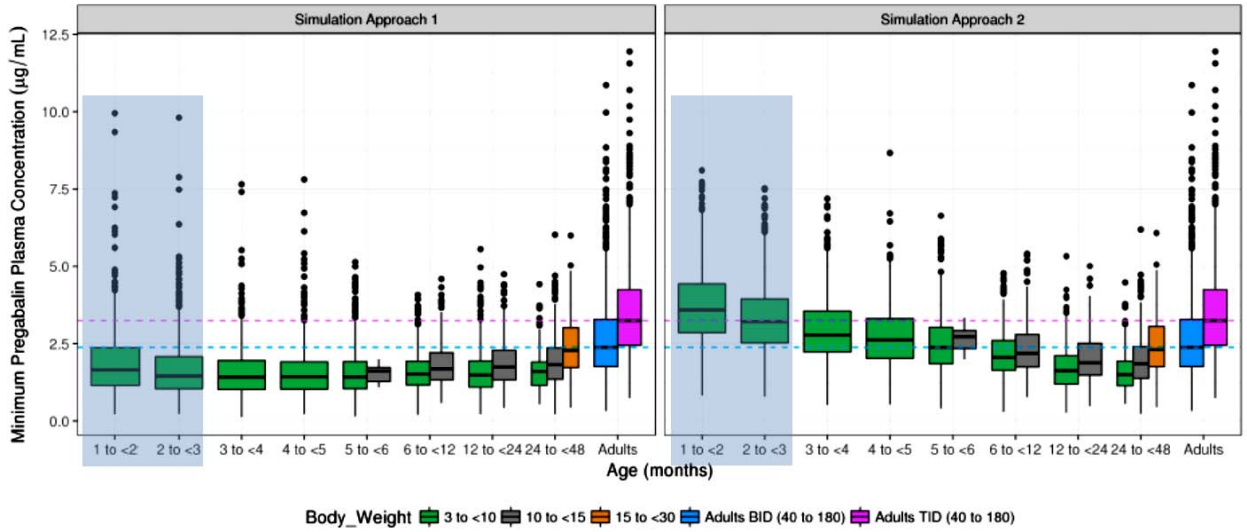
For pediatric subjects 1 year to < 4 years of age, the actual patients from Studies A0081074 and A00801042 within this age range at screening and under 30 kg of body weight were selected by sampling with replacement to preserve the correlations among covariates within the subjects. For pediatric subjects 1 month to <12 months of age, due to the lack of information from infants below the age of 3 months and the overall reduced number of subjects 3 to <12 months of age in the clinical studies, virtual subjects were created based on the demographic distribution by age group from the year 2000 CDC Growth Charts for the United States. One thousand pediatric subjects per age group (1000 subjects that are age 1 to < 2 years old and 1000 subjects that are age 2 to < 4 years old) were generated.

The simulation dataset for adult patients was created by sampling without replacement from the pool of 1040 adult patients age ≥ 17 years from Phase 3 studies (1008-009, 1008-011, and 1008-034) to a sample size of 1000 adult patients.

Individual PK parameters were used to predict pregabalin exposure ($C_{minss}$ , $C_{avss}$, and $C_{maxss}$) at the dosing regimen of 14 mg/kg/day for all age groups in pediatric subjects 1 month to <4 years of age. These exposures were compared to those in adult subjects with POS at the maximum approved dosing regimen (600 mg/day) (Figure 1, Figure 2, and Figure 3). Due to linear PK following multiple doses at 75 mg/day to 900 mg/kg, the Applicant conducted PK simulations for a single dose level.

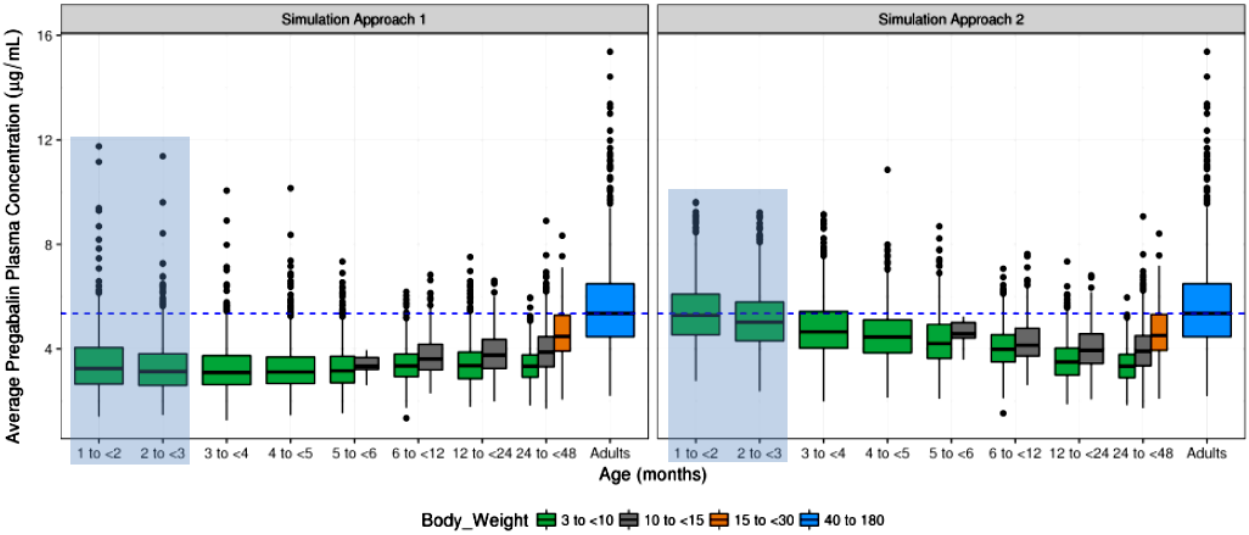
[1]Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ et al., 2009, Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatric nephrology vol. 24: 67.

**Figure 1: Simulated $C_{minss}$ for Adults (600 mg/day BID and TID) and Pediatric Patients Age 1 Month to 4 years (14 mg/kg/day TID) By Age and Weight Group**



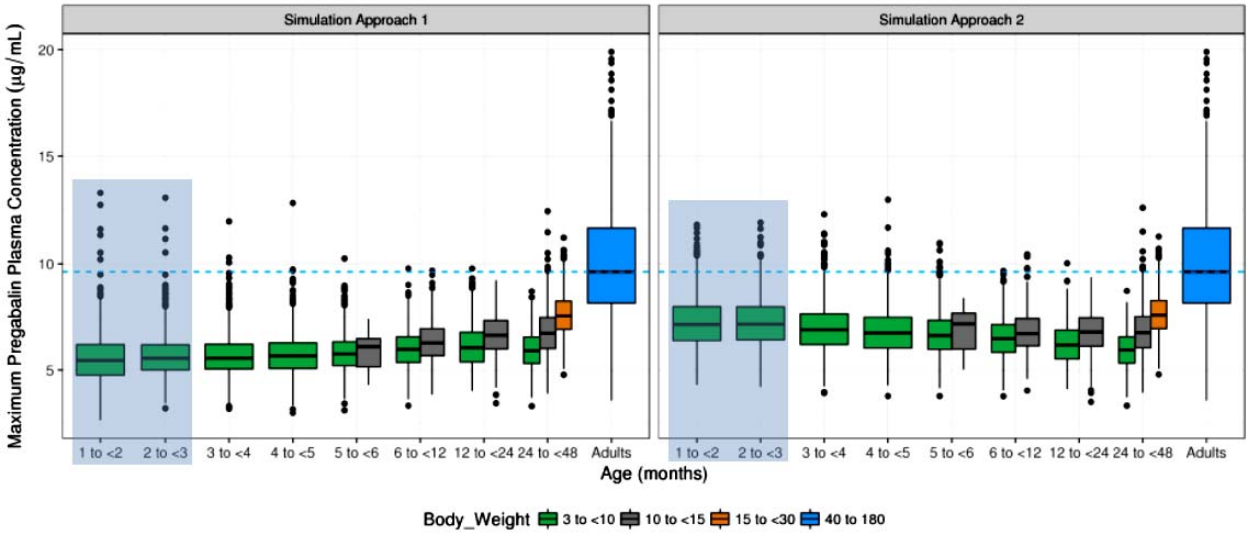

*The blue shaded boxes highlight the patient population of 1 to 2 months.*
*Pmar-eqdd-a008s-snda-689-supp.pdf, page 26 of 46.*

**Figure 2: Simulated $C_{avss}$ for Adults (600 mg/day BID) and Pediatric Patients Age 1 Month to 4 years (14 mg/kg/day TID) By Age and Weight Group**




*The blue shaded boxes highlight the patient population of 1 to 2 months.*
*Pmar-eqdd-a008s-snda-689-supp.pdf, page 24 of 46.*

**Figure 3: Simulated $C_{maxss}$ for Adults (600 mg/day BID) and Pediatric Patients Age 1 Month to 4 years (14 mg/kg/day TID) By Age and Weight Group**




*The blue shaded boxes highlight the patient population of 1 to 2 months.*
*Pmar-eqdd-a008s-snda-689-supp.pdf, page 25 of 46.*

The Applicant provides the following conclusions:

- In Simulation Approach 1, subjects 1 to < 3 months of age receiving 14 mg/kg/day had similar pregabalin exposures as those in older infants, whereas in Simulation Approach 2, subjects 1 to < 3 months of age had slightly higher pregabalin exposures than those in older infants.
- The $C_{maxss}$ in pediatric patients at the maximum proposed dose of 14 mg/kg/day TID did not exceed $C_{maxss}$ in adult subjects at the maximum approved dose of 600 mg/day BID.
- Due to the known PK linearity over the approved dose range, PK comparisons of 14 mg/kg/day in pediatric patients versus 600 mg/day in adults are expected to be similar to comparisons between lower approved dose levels with the "matching" pediatric dose level (e.g. 3.5 mg/kg/day in pediatric patients and 150 mg/day for adults).
- Overall, pregabalin dosages of 3.5 mg/kg/day to 14 mg/kg/day administered TID in pediatric subjects 1 month to <4 years of age achieve pregabalin exposure within the range of exposures in adult subjects at the matching approved dose range (i.e. 150 mg/day to 600 mg/day administered to adult subjects).

[*Reviewer comment: The Applicant's simulations are acceptable. The reviewer agrees that PK simulations at the highest dose levels in adult and pediatric patients (600 mg/day and 14 mg/kg/day, respectively) can inform simulations at lower dose levels (i.e. 150 mg/day and 3.5 mg/kg/day) due to the known PK linearity over this dose range.*

*Both simulation approach 1 and simulation approach 2 appear to produce PK profiles that support the 14 mg/kg/day TID regimen in pediatric patients age 1 to < 4 months. $C_{min}$ levels and*

*$C_{avss}$ levels are predicted to be either similar to pediatric patients > 4 months of age (Simulation Approach 1) or within the range observed in adults (Simulation Approach 2). $C_{max}$ levels in this population are predicted to be lower than the adult population due to the requirement for TID dosing in pediatric patients < 4 years of age. It is worth noting that the exposures in pediatric patients 4 months to 4 years at the 14 mg/kg/day dose (for which efficacy was established) were slightly lower than the exposures achieved in older pediatric patients or adult patients. Therefore, even though in pediatric patients 1 month to < 4 months of age receiving the same 14 mg/kg/day dose, the exposures are expected to increase (due to a lower degree of renal maturation) relative to pediatric patients > 4 months of age, the exposures are still within the range of those demonstrated to be safe in adults and older pediatric patients.*

*Overall, the two different approaches to modeling renal maturation produce different PK values yet both support the proposed 14 mg/kg/day TID dose regimen in pediatric patients age 1 to < 4 months.*

***Titration***

*Titration in Trial A0081042 occurred over a 5-day period. Neither the current approved Lyrica label nor the proposed Lyrica label in this supplement specify a duration for titration. The medical officer indicated that in practice, titration is likely to proceed with weekly dose increases such that it can take up to 6 weeks to reach the maximum dose. If a healthcare provider decided to titrate a one-month old patient over 6-week duration, then once titration is complete that patient would be nearly 3 months of age, and thus nearly the age of the patients enrolled in Trial A0081042. Thus, concerns about the lack of clinical experience of maintenance dosing in patients age 1 to 2 months are mitigated by titrating over a 6-week duration. In addition, the medical officer indicates that in the less common scenario where patients require more aggressive titration (i.e. dose increase every 3-5 days), the most common adverse event, somnolence, can be monitored. Please refer to the review from the Clinical discipline for details.*

***Selection of TID Dosing in Patients < 4 Years***

*The Applicant selected TID dosing in clinical trial A0081042 in patients age 1 month to < 4 years because the pregabalin $t_{½}$ was expected to be approximately 3 to 4 hours in pediatric patients in this age group which is shorter than the $t_{½}$ in older pediatric patients (age ≥ 4 years) or in adults. The clinical experience of the TID regimen in patients age 3 months to < 4 years supports the use of TID in this patient group (please refer to the review from the Clinical discipline for details). Use of TID dosing in patients age 1 to 2 months is supported by the Applicant's PK simulations.*

*Overall, the Applicant's proposed initiation dose level of 3.5 mg/kg/day, proposal to titrate based on effectiveness and tolerability, and proposed maximum recommended dose of 14 mg/kg/day, all in 3 divided doses (TID) for patients 1 month to younger than 4 years of age is acceptable*.]

## 6 LABEL STATEMENTS

OCP has the following comments regarding these key sections of the Applicant's proposed label language:

<table>
<tr><th>Applicant's proposed label statement language:</th><th>OCP Assessment</th></tr>
<tr><td>
2.4 Adjunctive Therapy for Partial Onset Seizures in Patients 1 Month~~4 Years~~ of Age and Older<br><br>
The recommended dosage for adults and pediatric patients 1 month~~4 years~~ of age and older is included in Table 1. Administer the total daily dosage orally in two or three divided doses. (b) (4)<br>
(b) (4)<br>
(b) (4) In pediatric patients ~~4 years of age and older~~, the recommended dosing regimen is dependent upon body weight. Based on clinical response and tolerability, dosage may be increased, approximately weekly.<br><br>
Table 1. Recommended Dosage for Adults and Pediatric Patients 1 Month~~4 Years~~ and Older (Module 2.7.2 SCP)
<table>
<tr><th>Age and Body Weight</th><th>Recommended Initial Dosage ~~(administer in two or three divided doses)~~</th><th>Recommended Maximum Dosage ~~(administer in two or three divided doses)~~</th><th>Frequency of Administration</th></tr>
<tr><td>Adults (17 years and older)</td><td>150 mg/day</td><td>600 mg/day</td><td>2 or 3 divided doses</td></tr>
<tr><td>Pediatric patients 4 years to younger than 17 years of age weighing 30 kg or more</td><td>2.5 mg/kg/day</td><td>10 mg/kg/day (not to exceed 600 mg/day)</td><td>2 or 3 divided doses</td></tr>
<tr><td>Pediatric patients 4 years to younger than 17 years of age weighing ~~11 kg to~~ less than 30 kg</td><td>3.5 mg/kg/day</td><td>14 mg/kg/day</td><td>2 or 3 divided doses</td></tr>
<tr><td>Pediatric patients 1 month to younger than 4 years of age</td><td>3.5 mg/kg/day</td><td>14 mg/kg/day</td><td>3 divided doses</td></tr>
</table>
Both the efficacy and adverse event profiles of LYRICA have been shown to be dose-related.<br><br>
The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.<br><br>
The efficacy of add-on LYRICA in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of LYRICA with gabapentin cannot be offered.
</td><td>Acceptable</td></tr>
<tr><td>Section 12.3, Pediatric Pharmacokinetics,<br>
Pediatric Patients (1 month ~~4~~ to less than 17 years of age)<br>
…<br>
A weight-based dosing regimen is necessary to achieve pregabalin exposures in pediatric patients aged ~~4 to~~ 1 month to less than 17 years similar to those observed in adults treated for partial onset seizures at effective doses [see Dosage and Administration (2.4)].</td><td>Section 12.3, Pediatric Pharmacokinetics,<br>
Pediatric Patients (3 months ~~4~~ to less than 17 years of age)<br><br>
Pregabalin PK were characterized in n=358 pediatric subjects ages 3 months to 16 years</td></tr>
</table>

The final label will reflect ongoing discussions within OCP, DNP, and with the Applicant after this review has been archived.

Michael Bewernitz, Ph.D.

**Reviewer, Division of Pharmacometrics (DPM)**

Dawei Li, Ph.D.

**Reviewer, Division of Clinical Pharmacology 1 (DCP1)**

Kevin Krudys, Ph.D.

**Team Leader, DPM**

Concurrence:

Angela Men, M.D., Ph.D._____

**Team Leader, DCP1**

cc: HFD-120 NDA# 022416/s-009

HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Dawei Li

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/s/

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MICHAEL A BEWERNITZ
04/26/2019 05:21:29 PM

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