Office of Clinical Pharmacology Review

sNDA#	NDA 022253/S-050, NDA 022254/S-040, NDA 022255/S-032 (NDA Efficacy Supplement set)
EDR location(s)	\\CDSESUB1\evsprod\NDA022254\0279 \\CDSESUB1\evsprod\NDA022253\0250 \\CDSESUB1\evsprod\NDA022255\0235
Submission Date(s)	06/30/2022
PDUFA Goal Date(s)	04/30/2023
Submission Type	Prior Approval Efficacy Supplement
Product Name	VIMPAT® (lacosamide)
Approved Dosage Forms	Tablets: 50, 100, 150, 200 mg (NDA 022253) Oral solution: 10 mg/mL (NDA (022255) Solution for intravenous infusion (10 mg/mL in 20 mL single-dose vial) (NDA 022254)
Approved Doses (all doses are BID)	Initial dosage: <50 kg: 1 mg/kg, ≥50 kg: 50 mg Maintenance dosage: 11 to ≤30 kg: 3-6 mg/kg, 30 to ≤50 kg: 2-4 mg/kg, >50 kg: 150-200 mg (monotherapy), 100-200 mg (adjunctive therapy)
Approved Indication	Monotherapy and adjunctive therapy for treatment of partial onset seizures (POS) in ≥1m and adjunctive therapy for treatment of primary generalized tonic-clonic seizures (PGTCS) individuals with idiopathic generalized epilepsy in ≥4y
Proposed Doses	Refer to Table 2 of this review
Applicant	UCB Biosciences, Inc.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OCP Review Team	Adarsh Gandhi, Ph.D. Atul Bhattaram, Ph.D. Gopichand Gottipati, Ph.D.

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1. Executive Summary

Lacosamide (VIMPAT®, LCM) is an antiepileptic agent, approved for treatment of partial-onset seizures in patients 1 month and older and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients 4 years and older. LCM is available in three dosage forms: film coated tablets for oral use, oral solution, and injection for intravenous use.

In this efficacy supplement, the applicant submitted data from Study EP0147, a retrospective cohort study (a Real-World Evidence Study, RWE) utilizing electronic health records (EHR) data (b) (4) from the PEDSnet clinical research network (PEDSnet.org). Briefly, PEDSnet data network integrates and standardizes health system EHR data across members into a common data repository, managed by a Centralized Coordinating Center at the Children's Hospital of Philadelphia. This study included 686 patients aged ≥1 month to <17 years and 28 neonates., The applicant used these data to support the use of an alternate dosing regimen to achieve the maintenance dosage in a shorter timeframe in pediatrics.

The primary review focus is to evaluate the appropriateness of the proposed alternate initial dosage regimen in pediatrics. Specifically, the review team conducted PK modeling and simulation in pediatric patients to compare the LCM PK profiles following the approved dosing regimen, i.e., without the initial loading dose (**Table 1)** and the newly proposed alternate dosing regimen, i.e., with initial loading dose (**Table 2**) over 8 weeks, which included dose initiation, titration and maintenance.

2. Office of Clinical Pharmacology Recommendations

The Office of Clinical Pharmacology (OCP) team reviewed the information submitted in NDA 022253/S-050 (with cross-reference to NDA 022254/S-040 and NDA 022255/S-032). OCP review team's exploratory PK analyses in pediatric patients showed that, at a mean level, LCM concentrations with the newly proposed alternate initial dosage, titration and maintenance regimen are higher than those following the currently approved regimen (i.e., without the alternate initial dosing regimen). The clinical relevance of these differences in exposures is unclear. Therefore, the OCP review team defers to the clinical team on the approvability of the proposed alternate initial dosage, titration and maintenance regimen based on the available information on LCM dosing and supportive safety data.

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Table 1 Approved LCM Dosing Schedule for Adults and Pediatric Patients ≥1 month for POS and PGTCS in Patients ≥4 years

Age and Body Weight	**Initial Dosage**	**Titration Regimen**	**Maintenance Dosage**
Adults (17 years and older)	**Monotherapy:** 100 mg twice daily (200 mg per day) **Adjunctive Therapy:** 50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 50 kg or more	50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 30 kg to less than 50 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)
Pediatric patients weighing 11 kg to less than 30 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)
Pediatric patients weighing 6 kg to less than 11 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)
Pediatric patients weighing less than 6 kg	IV: 0.66 mg/kg three times daily (2 mg/kg/day)	IV: Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	IV: 2.5 mg/kg to 5 mg/kg three times daily (7.5 mg/kg/day to 15 mg/kg/day)
	oral: 1 mg/kg twice daily (2 mg/kg/day)	oral: Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	oral: 3.75 mg/kg to 7.5 mg/kg twice daily (7.5 mg/kg/day to 15 mg/kg/day)

Table 2 Proposed LCM Dosing Schedule for Adults and Pediatric Patients ≥1 month for POS and PGTCS in Patients ≥4 years*

Age and Body Weight	Alternate Initial Dosage	Titration Regimen	Maintenance Dosage
Adults (17 years and older)	Single loading dose 200 mg 12 hours later initiate 100 mg twice daily (200 mg per day)	Increase by 50 mg twice daily (100 mg per day) at weekly intervals, if needed	**Monotherapy**** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing at least 50 kg	Single loading dose 200 mg 12 hours later initiate 100 mg twice daily (200 mg per day)	Increase by 50 mg twice daily (100 mg per day) at weekly intervals, if needed	**Monotherapy**** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 30 kg to less than 50 kg	Single loading dose 4 mg/kg 12 hours later initiate 2 mg/kg twice daily (4 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) at weekly intervals, if needed	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)
Pediatric patients weighing 11 kg to less than 30 kg Pediatric patients weighing 6 kg to less than 11 kg ±	Single loading dose 4.5 mg/kg 12 hours later initiate 3 mg/kg twice daily (6 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) at weekly intervals, if needed	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)
Pediatric patients weighing less than 6 kg ±	**Intravenous** No loading dose required 2.5 mg/kg three times daily (7.5 mg per day)	**Intravenous** Increase by 0.66 mg/kg three times daily (2 mg/kg/day) at weekly intervals, if needed	**Intravenous** 2.5 mg/kg to 5 mg/kg three times daily (7.5 mg/kg/day to 15 mg/kg/day)
	Oral No loading dose required 3.75 mg/kg twice daily (7.5 mg per day)	**Oral** Increase by 1 mg/kg twice daily (2 mg/kg/day) at weekly intervals, if needed	**Oral** 3.75 mg/kg to 7.5 mg/kg twice daily (7.5 mg/kg/day to 15 mg/kg/day)

Doses in Blue are proposed alternate initial doses for pediatric POS and PGTCS patients
*When not specified, the dosage is the same for monotherapy for partial-onset seizures and adjunctive therapy for partial-onset seizures or primary generalized tonic-clonic seizures. Oral and intravenous dosages are the same unless specified.
**Monotherapy for partial-onset seizures only
± indicated only for partial-onset seizures

3. Real World Evidence (RWE) study to support higher initial loading dose in pediatric patients

3.1. Background

On June 30, 2022, the Applicant submitted NDA 022253 (S050), and incorporated into NDAs 022254 (S040) and 022255 (S032) by means of cross-reference, the dataset for real-world evidence study EP0147, "Evaluating the Occurrence of Adverse Events Among Pediatric Patients Exposed to Intravenous Lacosamide (VIMPAT) Using Real World Data." Study EP0147 was a retrospective cohort study utilizing electronic health records data (b) (4) from the PEDSnet clinical research network. The PEDSnet data network integrates and standardizes health system EHR data across members into a common data repository, managed by a Centralized Coordinating Center at the Children's Hospital of Philadelphia. This data repository is used for feasibility testing, observational research, and patient recruitment into prospective studies, such as clinical trials.

Refer to Clinical review for further discussion on safety analysis of RWE data.

3.2. Applicant's Population PK Analysis – Study CL0447 Part IV

The applicant's population PK model was built with pediatric and adult PK data with data from several studies from the clinical development program. Refer to Clinical Pharmacology review for further discussion on Applicant's population PK model (DARRTS 10/05/2021). The Applicant's simulations focused on correspondence in exposure between adults and children. The dosing scheme used for these PK simulations were: 7.5 mg/kg bid oral dose or a 5 mg/kg tid IV dose for weight <6 kg, a 6 mg/kg bid oral dose for 6 kg to <30 kg, a 4 mg/kg bid dose for 30 kg to <50 kg, and a 200 mg bid dose for weight ≥ 50 kg. The PK simulations submitted by the Applicant are shown in Figure 1 below.

Figure 1: PK simulations with loading dose (LD) by weight bands

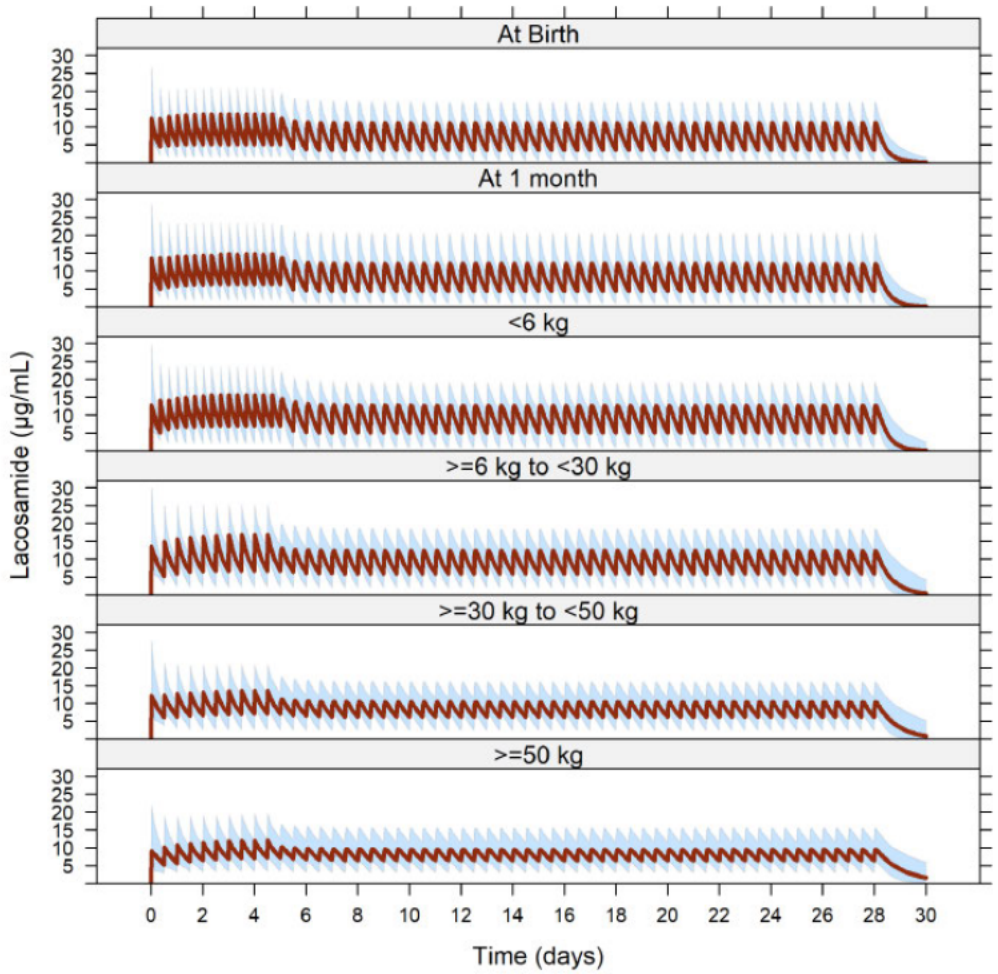


Figure 4 Add-on therapy: Time profile by weight bands using a 5 mg/kg tid iv dose for weight <6 kg, a 7.5 mg/kg bid oral dose for weight <6 kg, a 6 mg/kg bid dose for 6 kg<=weight<30 kg, a 4 mg/kg bid dose for 30 kg<=weight<50 kg, and a 200 mg bid dose for weight >=50 kg: the first dose given as a loading dose with 150% (for weights <30 kg) and 200% (for weights ≥30 kg) of the respective maintenance dose, for all age groups followed by oral administration
red line: median time profile, blue area: 90% of the simulated concentrations (from the 5th to the 95th percentile)

Source: cl0447-lacosamide-pk-report-part-iv-200923.pdf, page 16 of 124

Per the Applicant, "*these results suggest that the proposed dosing schedule of 7.5 mg/kg bid or 5 mg/kg tid for weight <6 kg, 6 mg/kg bid for weight ≥6 kg and weight <30 kg, 4 mg/kg bid for weight ≥30 kg and weight <50 kg, and 200 mg bid for weight ≥50 kg, results in uniform exposures across the investigated age and weight ranges in pediatric study participants.*

The investigation of adding of a loading dose (using 150% of the recommended maintenance dose for weights <30 kg and 200% of the recommended maintenance dose for weights ≥30 kg) resulted in LCM concentrations similar to steady state concentrations from treatment start onwards."

3.3 Reviewer's Independent Analyses

The Applicant's PK simulations spanned a duration of up to 28 days only, whereas the dosing regimen for LCM entails initial-, titration and maintenance dosing can span up to 8 weeks. The OCP review team conducted exploratory PK simulations across different pediatric age and bodyweight groups using the approved and proposed doses. The OCP review team referred to the equations below for generating initial parameter estimates for CL and V. For simulations, median body weight in each cohort was used as representative subjects.

$$CL = 1.74 \cdot e^{\eta_{CL,i} + 0.467*log\left(WT_i/70\right) + 0.251*InducerAED - 0.164*China - 0.129*Japan + \log\left(\frac{\left(Age+\frac{9}{12}\right)^{Hill}}{Mat^{Hill}+\left(Age+\frac{9}{12}\right)^{Hill}}\right)}$$

where Inducer AED, China, and Japan are 1 when present and 0 otherwise, Mat is age at 50% maturation, Hill is Hill coefficient,

$$Vc = 45.4 * e^{\eta_{Vc,i} + 1.00*log\left(WT_i/70\right)}$$

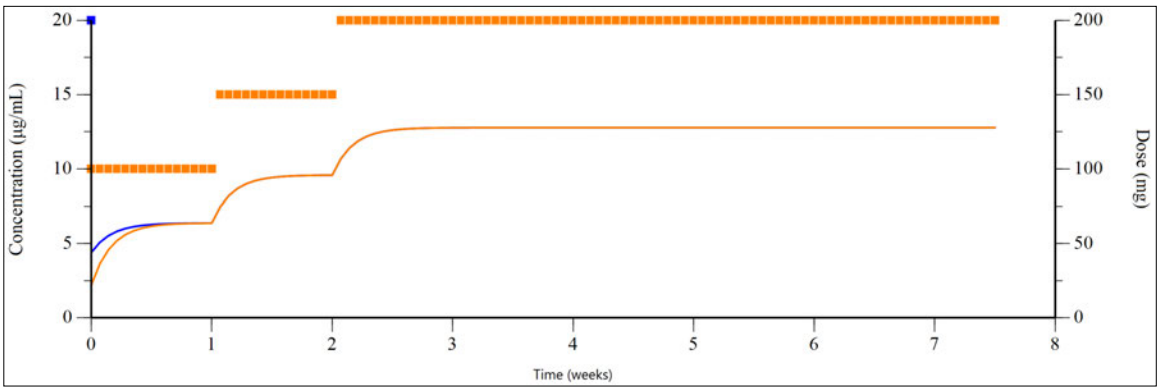
Based on the equations above, the initial estimates for CL and V are displayed in the table below.

No.	Cohort	Median body weight (kg)	Median age (years)	CL (L/h)	V (L)
1.	Adult	70	20.0	1.60	45.4
2.	≥50kg	50	14.0	1.34	32.4
3.	30 to <50 kg	40	11.9	1.20	25.9
4.	11 to <30 kg	20	5.71	0.81	12.9
5.	6 to <11 kg	8.5	0.63	0.40	5.51
6.	<6kg	4	0.04	0.24	2.60

Source: Reviewer generated initial parameter estimates

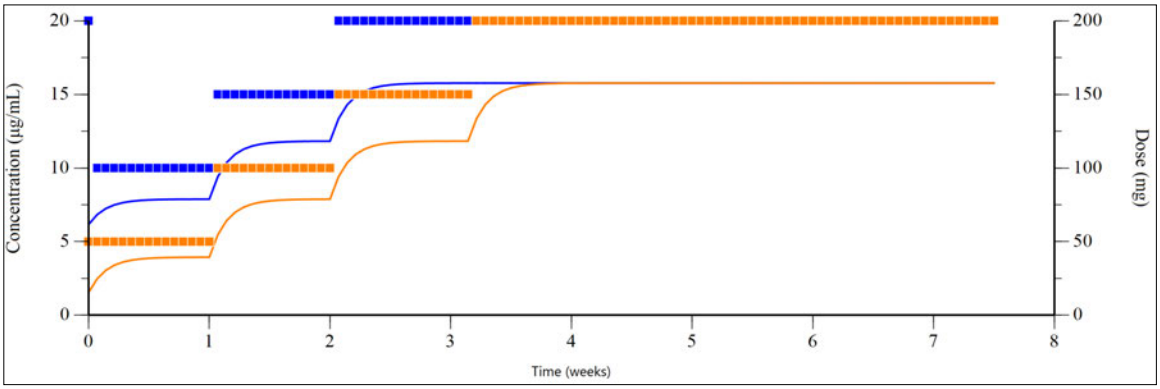
The OCP review team's PK simulations from all the above cohorts are presented in Figures 2-1 to 2-6. The simulations were generated using dosing regimen from Tables 1 and 2. For each figure, line represents LCM conc in µg/mL and box represents LCM dose in mg. The orange color represents approved doses (no loading dose) and the blue color represents proposed doses (with alternate initial loading dose).

Figure 2-1: PK simulations in adults



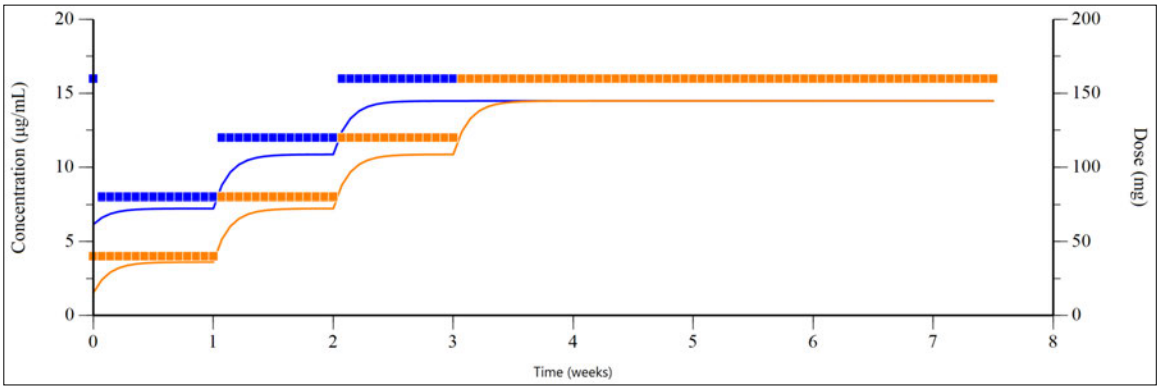
Dosing regimen in orange boxes: Week 1: 100 mg BID, Week 2: 150 mg BID, Week 3: 200 mg BID
Dosing regimen in blue boxes: Week 1: 200 mg single LD followed 12h later by 100 mg BID, Week 2: 150 mg BID, Week 3: 200 mg BID

Figure 2-2: PK simulations in ≥50kg



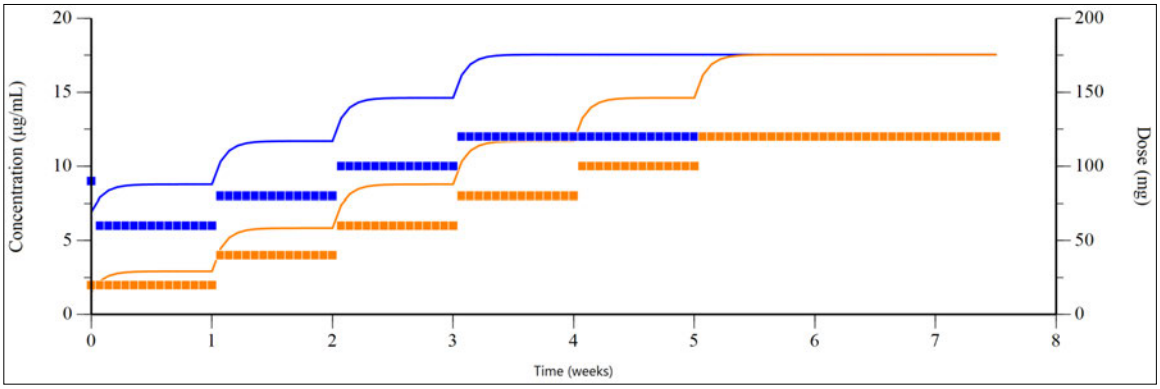
Dosing regimen in orange boxes: Week 1: 100 mg BID, Week 2: 150 mg BID, Week 3: 200 mg BID
Dosing regimen in blue boxes: Week 1: 200 mg single LD followed 12h later by 100 mg BID, Week 2: 150 mg BID, Week 3: 200 mg BID

Figure 2-3: PK simulations in 30 to <50kg



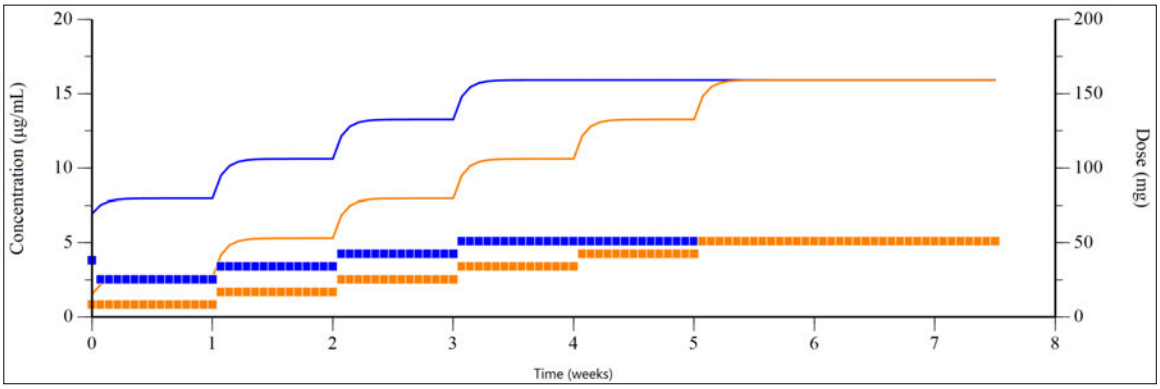
Dosing regimen in orange boxes: Week 1: 1 mg/kg BID, Week 2: 2 mg/kg BID, Week 3: 3 mg/kg BID, Week 4: 4 mg/kg BID
Dosing regimen in blue boxes: Week 1: 4 mg/kg single LD followed 12h later by 2 mg/kg BID, Week 2: 3 mg/kg BID, Week 3: 4 mg/kg BID

Figure 2-4: PK simulations in 11 to <30kg



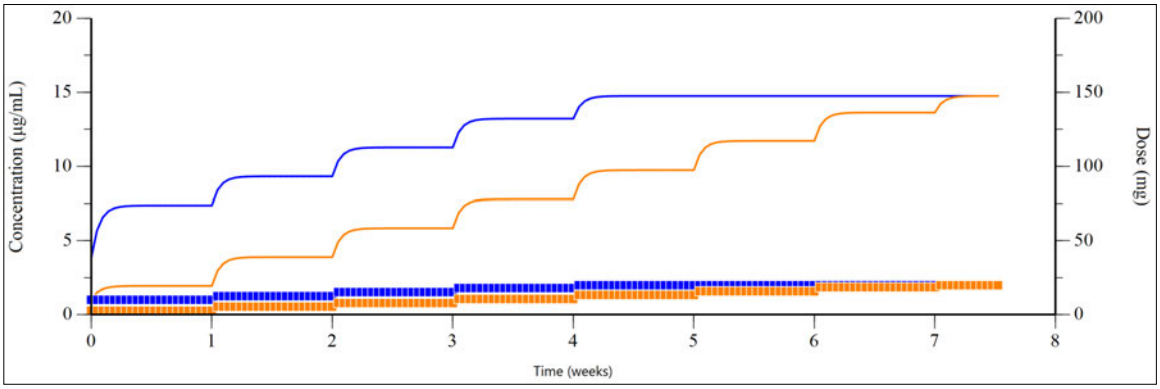
Dosing regimen in orange boxes: Week 1: 1 mg/kg BID, Week 2: 2 mg/kg BID, Week 3: 3 mg/kg BID, Week 4: 4 mg/kg BID, Week 5: 5 mg/kg BID, Week 6: 6 mg/kg BID
Dosing regimen in blue boxes: Week 1: 4.5 mg/kg single LD followed 12h later by 3 mg/kg BID, Week 2: 4 mg/kg BID, Week 3: 5 mg/kg BID, Week 4: 6 mg/kg BID

Figure 2-5: PK simulations in 6 to <11kg



Dosing regimen in orange boxes: Week 1: 1 mg/kg BID, Week 2: 2 mg/kg BID, Week 3: 3 mg/kg BID, Week 4: 4 mg/kg BID, Week 5: 5 mg/kg BID, Week 6: 6 mg/kg BID
Dosing regimen in blue boxes: Week 1: 4.5 mg/kg single LD followed 12h later by 3 mg/kg BID, Week 2: 4 mg/kg BID, Week 3: 5 mg/kg BID, Week 4: 6 mg/kg BID

Figure 2-6: PK simulations in <6kg



Dosing regimen in orange boxes: Week 1: 0.66 mg/kg TID, Week 2: 1.32 mg/kg TID, Week 3: 1.98 mg/kg TID, Week 4: 2.64 mg/kg TID, Week 5: 3.3 mg/kg TID, Week 6: 3.96 mg/kg TID, Week 7: 4.62 mg/kg TID, Week 8: 5.28 mg/kg TID
Dosing regimen in blue boxes: Week 1: 2.5 mg/kg TID, Week 2: 3.16 mg/kg TID, Week 3: 3.82 mg/kg TID, Week 4: 4.48 mg/kg TID, Week 5: 5.14 mg/kg TID

PK simulations demonstrate higher LCM concentrations in all pediatric body weight cohorts with alternate dosing scenario (with initial loading dose) compared to without the initial loading dose. These PK simulations with the proposed dosing regimen were presented to the Clinical review team to contextualize the available dosing records and safety data submitted by the applicant in determining the appropriateness of the newly proposed dosing regimen.

3.4 Conclusion

OCP review team's exploratory PK simulations were conducted to cover the duration of dosing, which includes dose initiation, with and without new proposed alternate initial dosing, titration, and maintenance over 8 weeks, unlike the applicant's simulations which spanned only over 28 days. OCP team's exploratory PK simulations in pediatric patients showed, at a mean level, LCM concentrations following the newly proposed regimen, are higher than those following the currently approved regimen (i.e., without the alternate initial dosing regimen). The clinical relevance of these differences in exposures is unclear. Therefore, the OCP review team defers to the clinical team on the approvability of the proposed alternate initial dosage, titration and maintenance regimen based on any available dosing records for the proposed dosing from the RWE study and supportive safety data.

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