Bioequivalence Analysis of Lamotrigine Extended-Release (ER) Tablets based on an In Vitro-In Vivo Relationship (IVIVR) Using the Physiologically Based Pharmacokinetic (PBPK) Absorption Model

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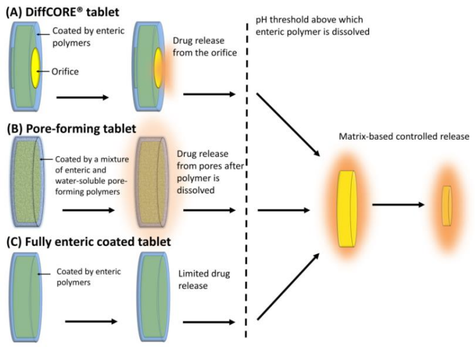
PURPOSE

- Lamictal XR (lamotrigine ER tablets at strengths of 25, 50, 100, 200, 250, 300 mg) is a second generation anti-epilepsy drug (AED) taken once daily with or without food, indicated for the treatment of seizure control.
- As of June 2016, FDA has approved 8 generic copies of lamotrigine ER tablets which employ different controlled release mechanisms (see Figure below) from the reference listed drug (RLD) product owing to patent protection (DiffCORE).



- To demonstrate bioequivalence (BE) between generic lamotrigine ER tablets and the RLD, generic applicants are recommended to conduct single-dose, two-way, crossover BE studies in healthy subjects comparing the test products at 50 and 200 mg strengths with RLD, and other strengths may be eligible for waiver of in vivo studies if they meet all the criteria in product-specific guidance.
- This study aims to (1) based on formulation and dissolution analyses, evaluate the brand-to-generic BE for the strengths where in vivo BE studies were not conducted using a PBPK model as a prediction of the clinical significance of the dissolution differences (i.e. confirming a minimal risk of generic substitution at multiple strengths), and (2) select a generic product for a to-be-conducted post-market PK BE study representing the worst-case scenario of generic switching.

METHOD

- Generic A and B that are currently available on the market have been identified for simulation based on two criteria: (1) formulation proportionality and (2) in vitro dissolution of Test/RLD and Test/Test across all strengths.
- To develop an IVIVR, GastroPlus® (Simulations Plus Inc. Lancaster, CA) based on the ACAT (Advanced Compartmental Absorption and Transit) simulation model was used to perform PBPK modeling for the prediction of in vivo lamotrigine PK profiles. In vitro dissolution and in vivo PK data were collected from multiple Abbreviated New Drug Applications (ANDAs).
- Dissolution testing was conducted using a new dissolution method to simulate the pH transition of human gastrointestinal tract under fed conditions.
- The PBPK model was used to predict the in vivo PK profiles of the Generic A and B products at 50-200 mg administered with food using their dissolution profiles in support of a to-be-conducted post-market PK BE study.

RESULTS

Assessing Strengths Waived for In Vivo BE Studies

- Generic A and B were identified based on formulation proportionality and comparative dissolution testing (Table 1).

Table 1. Formulation proportionality and comparative dissolution

	BE strength	Formulation proportionality SUPAC-MR change		F2 test for Dissolution	
		Non-release controlling excipient	Release controlling excipient	Test vs. RLD	Test vs. Test (BE vs. waived strengths)
RLD	N/A	Level 1 (all vs. 50 mg)	Level 2 (25 vs 50 mg); Level 3 (100-300 vs 50 mg)	N/A	N/A
Generic A	50 mg	No change	Level 3 (100-300 vs 50 mg)	25/25 mg: 55 50/50 mg: 73 100/100 mg: 84 200/200 mg: 75 250/250 mg: 78 300/300 mg: 55	50/25 mg: 55 50/100 mg: 39 50/200 mg: 55 50/250 mg: 46 50/300 mg: 70
Generic B	50, 200 mg	Level 1	Level 3 (100 vs. 200 mg)	25/25 mg: 81 100/100 mg: 72 300/300 mg: 69	50/25 mg: 87 200/100 mg: 69 200/300 mg: 85

IVIVR Development

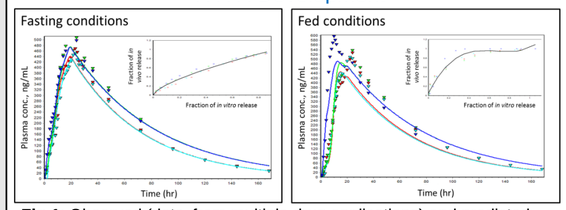


Fig 1: Observed (dots, from multiple drug applications) and predicted (lines, PBPK models) PK profiles of a single-dose 50-mg lamotrigine ER tablets under fasting and fed conditions. Inset: IVIV relationship

- The model adequately predicted the observed PK profiles of single-dose 50-mg lamotrigine in humans under fasting/fed conditions (Fig 1).
- An IVIVR between in vitro dissolution profiles and deconvoluted in vivo drug release was successfully established (insets of Fig 1).
- A new dissolution method (Table 2, fed) was proposed to simulate the fed condition. The Fasting dissolution method is compendial. The dissolution profiles of RLD and Generic A and B are shown in Fig 2.

Table 2. A new dissolution method simulating fasting and fed conditions

	Stage 1	Stage 2
Fasting	2 hrs in 0.01 N HCl	20 hrs in pH 6.8 phosphate buffer with 2.25%SLS
Fed	6 hrs in pH 4.5 buffer	16 hrs in pH 6.8 phosphate buffer with 2.25%SLS

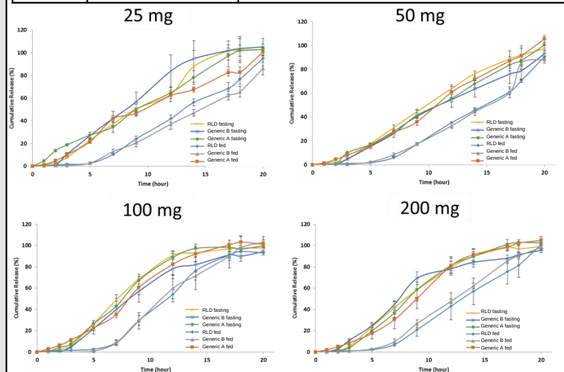


Fig 2. 25, 50, 100, and 200 mg of RLD, Generic A and B cumulative release using the new fasting and fed dissolution methods.

Simulated BE Studies

- The established PBPK model was used to simulate BE studies comparing RLD and Generic A or B after a single-dose administration of 25-200 mg lamotrigine ER tablets in 24 healthy subjects under fed conditions (Fig 3).

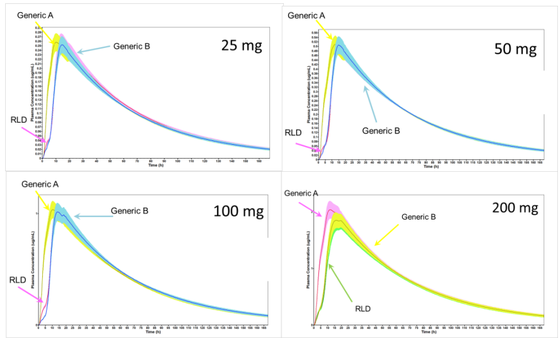


Fig 3. PBPK modeling of single-dose fed BE studies comparing 25, 50, 100, and 200 mg of RLD vs. Generic A or B lamotrigine ER tablets. The shaded areas are 90%CI.

- An inter-subject variability of 20% for volume of distribution (Vd) and 40% clearance was used for the single-dose BE simulation. The Test/RLD ratio with 90% confidence intervals (CI) of predicted PK metrics (i.e. Cmax and AUCt) for the generic lamotrigine ER tablets were entirely within the bioequivalence acceptance limits (i.e. 80%-125%) at 25-200 mg under fed conditions (Table 3).
- Although the F2 values for dissolution testing of Generic A at 100 and 250 mg vs. the BE strength (50 mg) are <50 (Table 1), the simulated PK results show BE between Generic A and the RLD (Table 3).

Table 3. Summary of PK metrics in simulated fed BE study (Fig 2)

Strength	Generic	AUC_{inf}		AUC_t		C_{max}	
		PE	90%CI	PE	90%CI	PE	90%CI
25 mg	A	101.23	100.3-102.2	101.7	100.8-102.6	99.86	95.6-104.4
	B	96.1	95.1-97.1	96.0	95.0-96.9	94.7	93.7-102.0
50 mg	A	105.6	104.7-106.6	106.1	104.9-10.4	101.2	96.4-106.2
	B	100.5	99.4-101.6	100.5	99.1-101.8	100.3	95.5-105.3
100 mg	A	104.5	103.1-105.8	105.1	103.6-106.5	100.8	96.1-105.8
	B	100.8	99.7-101.9	100.7	99.4-102.1	99.6	94.6-104.9
200 mg	A	110.7	107.7-113.9	109.7	103.6-116.2	111.4	108.4-114.5
	B	102.3	101.1-103.4	102.4	100.8-103.9	102.1	96.4-108.2

Passing Ratio (%) for Lamotrigine Virtual BE Trials

- In virtual clinical trials, 1000 times of (12-72 subjects) in a pool of 1000 simulations were randomly chosen. The BE passing ratio (%) (i.e. T/R ratio with 90%CI within 80-125%) of PK metrics was calculated based on 5% or 10% intra-subject CV in single-dose (Table 4) and multiple-dose (Table 5) studies.
- With a 5% intra-sub CV and N≥36 , Generic A and B show a BE passing score >~47% when in a single-dose fed BE study at 25-200 mg (Generic A slightly lower than B), and >~76% in a multiple-dose fed BE study.

0% 100%

25 mg	50 mg
100 mg	200 mg

Table 4. BE passing ratio (%) of Cmax, AUC_{inf} and AUC_{0-t} in **single-dose** fed BE studies comparing 25-200 mg RLD vs Generic A (upper panel) or B (lower panel) in randomly picked 1000 trials of N (number of subjects) among 1000 simulations

N	5% intra-sub variability						10% intra-sub variability					
	Cmax		AUC_{inf}		AUC_{0-t}		Cmax		AUC_{inf}		AUC_{0-t}	
12	93.1	86.3	25.4	21.2	26.5	21.6	19.7	9.7	0.8	0.4	0.9	0.4
	75.8	42.1	14.9	8.3	14.7	8.1	4.8	2.4	0.3	0	0.3	0
24	100	99.6	69.3	63.5	67.9	63	66.7	52.1	3.4	1.6	4.2	1.6
	98.3	72.9	61.5	34.2	58.9	33.2	32.3	17.8	0.6	0.3	0.7	0.4
36	100	100	82.5	79.5	81.7	77.8	87.6	78.2	14.7	10.9	14.4	11.1
	99.9	86.8	82.4	49.6	81	47.7	65.8	36.6	4.9	2.1	5.8	2.1
48	100	100	92.7	89.4	91.9	88.9	95.1	91.9	32.3	23	32.6	23.6
	100	94.6	91.8	60.4	90.7	57.6	82.2	55	17.4	8.5	19.3	8.5
72	100	100	98.1	96.6	97.8	96.1	99.5	98.3	4.8	96.6	53.9	96.1
	100	99.3	97.9	75.6	97.6	71.7	95.6	69	43.7	26.5	44.7	26.2
N	5% intra-sub variability						10% intra-sub variability					
	Cmax		AUC_{inf}		AUC_{0-t}		Cmax		AUC_{inf}		AUC_{0-t}	
12	94.9	87.5	30.7	23.4	32.1	24.4	22.2	10.8	0.5	0.2	0.6	0.3
	76.4	67.6	22	13.8	22.8	14.5	5.4	3.6	0.1	0	0.1	0
24	100	99.9	77.5	74.7	78.7	75.9	66.3	51.5	3.2	1.7	3.2	1.9
	98.9	96.9	64.8	57.7	65.7	58.4	38.1	24.9	0.5	0.1	0.5	0.1
36	100	100	93.3	92.3	93.7	92.8	89.5	80.9	16.7	12.5	17.9	13.4
	100	99.8	88.6	85	89.4	86.1	72	54.1	4.9	2.7	5.2	3
48	100	100	97.3	97.9	97.7	97.9	96.4	92.5	37.7	27.7	39.7	29.1
	100	100	96.2	93.5	96.8	93.5	83.4	72.5	19.7	10.5	20.5	11.5
72	100	100	99.8	99.9	99.8	99.9	99.9	98.7	63.2	99.9	64.5	60.2
	100	100	99.5	99.2	99.5	99.4	96.8	90.1	47.8	42	48.8	42.8

Table 5. BE passing ratio (%) of Cmin,ss (steady-state), Cmax,ss, and AUC_τ (216-240 hr) in **multiple-dose** fed BE studies comparing 25-200 mg RLD vs Generic A (upper panel) or B (lower panel) in randomly picked 1000 trials of N (number of subjects) among 1000 simulations

N	Intra-sub variability 5%						Intra-sub variability 10%					
	Cmin,ss		Cmax,ss		AUC_τ		Cmin,ss		Cmax,ss		AUC_τ	
12	79	65.5	67.1	61.4	27.9	21.2	6.8	3.7	6.4	2.9	0.2	0
	60.4	42.7	54.6	31.1	16.8	10.4	2.5	2	2.1	0.8	0.4	0.1
24	96.8	93	89.5	91.7	62.2	57.3	42.4	30.6	33.4	27	2.6	2.3
	94.3	83.5	91.7	59.6	59.7	38.1	16.8	10.8	14.4	7.2	0.3	0.1
36	99.6	98.7	98.3	98.1	77.8	74.5	67.3	56.1	53.6	52.5	14.8	11.8
	99.4	95.8	98.5	76.4	91.9	56.2	47.6	33.5	43.4	22.1	5.3	2.2
48	100	100	99.3	99.8	90.1	87	83.2	71	65.7	68.4	29.2	23
	99.9	98.7	99.4	85	92.8	66	68.2	50.3	63.2	33.2	16.5	7.6
72	100	100	100	100	96.8	47.4	94.7	88.9	83.9	86.1	51.6	3.6
	100	100	100	95.4	98.4	83.1	88.2	77.3	83.7	52.3	43.8	27.2
N	Intra-sub variability 5%						Intra-sub variability 10%					
	Cmin,ss		Cmax,ss		AUC_τ		Cmin,ss		Cmax,ss		AUC_τ	
12	74.6	84.3	75.6	79.8	44.2	43.7	30.4	39.7	21.5	23.3	2.3	0.9
	80.9	81.7	81.9	76.2	35.7	29.8	33.3	33.2	19.4	15.6	0.4	0.2
24	95.3	98.4	95.7	97.4	75.9	84.7	53.6	63	51.2	54.1	18.2	10.9
	97.7	97.7	98.1	96.5	83.8	77.4	57.5	56.5	51.8	44.4	3.9	1.9
36	99.8	99.6	99.8	99.6	90.9	94.1	69.3	80.1	68.9	74.4	38.8	32.8
	99.7	99.7	99.7	99.5	95.7	94.2	75.2	72.7	73.6	64.6	19.6	12.8
48	99.9	100	99.9	100	96.9	98.5	80.1	88.8	80.7	84.7	49.6	51.9
	100	99.9	100	99.9	98.7	97.6	85.3	82.6	85.7	77.2	44	32.1
72	100	100	100	100	99.9	100	92	96.6	92.5	95.4	68	73
	100	100	100	100	100	99.9	94.7	96	95.4	94.2	72.6	59.9

CONCLUSION

- Based on the single-dose PK simulations, generic lamotrigine ER tablets with a different release mechanism from the RLD appear to conform to the bioequivalence requirements of PK metrics (i.e. Cmax and AUCt) at strengths waived for in vivo BE studies.
- In the current study, virtual clinical trials based on PBPK modeling and simulation appear to be a powerful tool to predict PK profiles at strengths waived for in vivo BE studies and to confirm a minimal substitution risk of the generic drug products at 25-200 mg.
- RLD and Generic A (200 mg) were selected for the prospective clinical PK BE study to bracket the worst case scenario.

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- Disclaimer: This article reflects the views of the authors and should not be construed to represent the FDA's views or policies.