3.212 - 67th Annual Meeting of the American Epilepsy Society 2013 (Washington, DC)

Comparison of Bioavailability and Dissolution Data for Generic Lamotrigine Tablets in the Equigen Trial

T Welty,[1] E Elder,[2] A Schuelke,[2] K Jones,[2] B Gidal,[2] P Bolger,[3] R Alloway,[4] M Privitera,[4] M Berg[3]

[1]Drake University, [2]University of Wisconsin, [3]University of Rochester, [4]University of Cincinnati

Rationale:

As part of the Equigen study, disparate generic lamotrigine (LTG) products were selected for both arms of the study. This selection was based upon bioavailability data from ANDA applications for LTG products, and dissolution, content, and purity analysis in an independent lab of selected generic LTG products purchased on the open market.

Methods:

Using information on market availability of various generic LTG products, several products in the 25 mg and 100 mg tablet strengths were selected for dissolution, content uniformity (CU), and purity testing by an independent laboratory. CU was determined using the acceptance value (AV), with higher AV indicating more variability in content. Generic products A-F are 25 mg tablets. Generic products V-Z are 100 mg tablets. For 100 mg tablets, multiple lots from some manufacturers were tested. Bioavailability data from original ANDA applications were supplied by the FDA for all generic LTG products. Comparisons between bioavailability and in-vitro data were made to determine which products were above or below the mean of the branded product. These comparisons were used to determine the disparate generic products for the Equigen study. The ANDA data that was used is based upon the tablet strength and dose that was used in the manufacturer's ANDA submission. These strengths or doses may be different than a single 25 mg or 100 mg tablet. However, only FDA approved 25 mg or 100 mg tablets were used in the dissolution studies.

Results:

Products E and V, C and X, D and Y, and F and Z are from the same manufacturers.

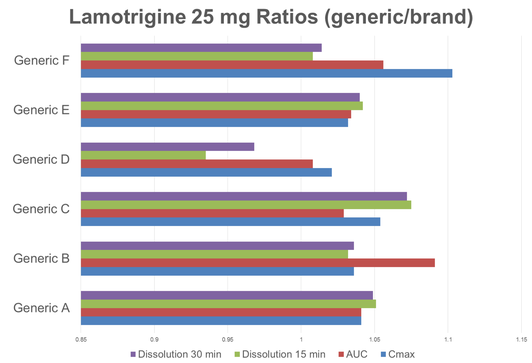
Lamotrigine 25 mg Products

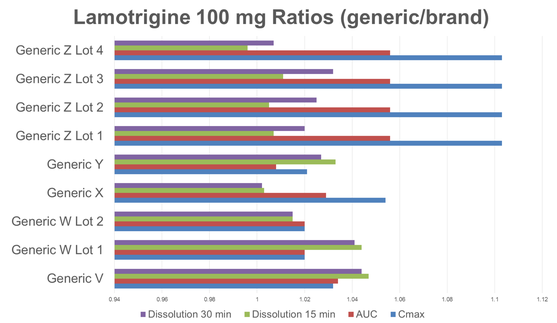
Product	ANDA Strength	ANDA Cmax Ratio (90% CI)	ANDA AUC Ratio (90% CI)	Dissolution at 15 min (%)	Dissolution at 30 min (%)	Content Uniformity Acceptance Value
Brand				97.0	97.2	4.24
Generic A	200 mg	1.041 (99.99-108.47)	1.041 (101.33-106.89)	101.9	102.0	11.58
Generic B	200 mg	1.036 (100.8-105.8)	1.091 (102.7-115.9)	100.1	100.7	7.31
Generic C	25 mg	1.054 (101.15-109.86)	1.029 (99.46-106.45)	104.3	104.2	4.83
Generic D	2x25 mg	1.021 (97.7-107.9)	1.008 (96.6-105.3)	90.7	94.1	5.2
Generic E	2x25 mg	1.032 (98.71-107.86)	1.034 (98.19-108.81)	101.1	101.1	4.68
Generic F	25 mg	1.103 (104.75-116.10)	1.056 (98.32-113.4)	97.8	98.6	4.91

Lamotrigine 100 mg Products

Product	ANDA Strength	ANDA Cmax Ratio (90% CI)	ANDA AUC Ratio (90% CI)	Dissolution at 15 min (%)	Dissolution at 30 min (%)	Content Uniformity Acceptance Value
Brand				97.2	97.6	7.04
Generic V	2x25 mg	1.032 (98.71-107.86	1.034 (98.19-108.81)	101.8	101.9	4.22
Generic W Lot 1	2x25 mg	1.020 (96.52-107.78)	1.020 (99.81-104.23)	101.5	101.6	3.72
Generic W Lot 2				98.7	99.1	8.41
Generic X	25 mg	1.054 (101.15-109.86)	1.029 (99.46-106.45	97.5	97.8	10.1
Generic Y	2x25 mg	1.021 (97.7-107.9)	1.008 (96.6-105.3)	100.4	100.2	7.89
Generic Z Lot 1	25 mg	1.103 (104.75-116.10)	1.056 (98.32-113.4)	97.9	99.6	8.71
Generic Z Lot 2				97.7	100.0	6.79
Generic Z Lot 3				98.3	100.7	4.11
Generic Z Lot 4				96.8	98.3	4.44

Comparisons of Generic Products to Branded Product





SUMMARY

1. FDA standards allow for approval of a generic product based on dissolution testing if a larger strength of the product is identical in formulation and was approved using bioequivalency testing.
2. Selection of disparate products was difficult due to various strengths used in ANDA submissions.
3. Discrepancies between ANDA pharmacokinetic and our dissolution data confounded product selection.
4. Dissolution values for products C and X and D and Y, where different strengths from the same manufacturer were tested, showed a great amount of variability between 25 mg and 100 mg strengths.
5. Branded lamotrigine consistently had dissolution rates <100%.

CONCLUSION

1. Comparisons of differences between generic products and the brand product did not provide results that were consistently in the same direction.
2. Variability in dissolution testing of different strengths of the same generic product for some manufacturers is concerning.
3. It is unclear if results would be different had the ANDA data and dissolution testing been done using the same tablet strengths.

Funded by a Prime grant to FEFA, LLC is from Funding Entity: U.S. Department of Health and Human Services/Food and Drug Administration/Office of Acquisitions and Grants Services/Division of Contracts and Grants Management (DHHS/FDA/OAGS/DCGM).