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Identification of the Most Disparate Generic Lamotrigine Tablets Based on *in vitro* Screening

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Introduction

Lamotrigine is a narrow therapeutic index drug for the treatment of epilepsy. Narrow therapeutic index drugs are often implicated in having variable patient response when switching manufacturer.

The purpose of this work was to conduct *in vitro* analysis of various lots of lamotrigine in order to select products with the greatest possible difference in product performance. The evaluation was performed on ten generic 100-mg tablet lots and eight generic 25-mg tablet lots, plus one lot of each strength of the branded product, following the lamotrigine tablet monograph from the United States Pharmacopoeia (USP 34), which includes assay, impurities, dissolution, and uniformity of dosage unit tests.

A method for selecting the most disparate generics for use in a clinical investigation was determined based the sum of differences in rank order for results of *in vitro* testing along with formulation composition and available bioequivalence data from ANDA submissions.

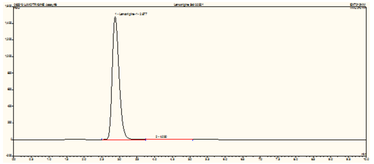
Materials

Lamotrigine 25 mg tablets (Lamictal®, Lot # 2ZP5874, GSK)

Lamotrigine 100 mg tablets (Lamictal®, Lot # 2ZP1693, GSK)

Generic products are blinded until completion of the EQUIGEN* clinical study. The six 25 mg products initially tested were each from different manufacturers and the ten 100 mg lots represented five manufacturers.

Figure 1 – Example Lamotrigine HPLC Chromatogram



Methods

Assay

The potency, impurities and content uniformity of lamotrigine tablets were measured by high performance liquid chromatography (HPLC) following the lamotrigine monograph assay. The acceptance criterion for potency states that the assay result must be 90.0 – 110.0%.

HPLC Analytical Method

The HPLC conditions used for sample analysis were:

- Column: C18, 5µm, 150 x 2.1mm
- Column Temperature: 25ºC
- Injection volume: 10 µL
- Flow Rate: 0.2 mL/min
- Detector: 210 nm
- Buffer: 0.77g/L ammonium acetate, adjusted to pH 4.5 with glacial acetic acid.
- Mobile Phase: methanol / buffer, 60:40.
- Pump program: Isocratic

The appropriateness of the USP method conditions was verified by demonstrating that the analytical system suitability criteria were satisfied. A representative chromatogram from a standard injection is shown in Figure 1.

Dissolution

Dissolution of lamotrigine tablets was performed following USP dissolution general chapter <711> and the lamotrigine tablet monograph in USP 34. The following conditions were used:

- Media Volume: 900 mL
- Apparatus: II (paddles) with 1-L vessels
- Rotation Speed: 50 rpm
- Bath Temperature: 37 ± 0.5ºC
- Timepoints: 5, 10, 15, 20, 25, and 30 min. (D30)

Calculations

Content (C) is an average assay value based on a composite sample, Content Uniformity (CU) is an average assay value based on analysis of individual tablets. Acceptance Value (AV) is a statistical analysis of the CU variability with a limit of 15. A higher AV indicates more variable content.

Experimental Design

Results for each analysis were rank ordered (Tables 1 & 2) and the difference between the rank of each result was calculated. The sum of the differences from all analyses for each product was obtained to determine the products with the greatest difference for *in vitro* performance.

Table 1 – 25 mg Rank Order

25 mg	Lamotrigine Tablets			
Code	**C-Rank**	**CU-Rank**	**AV-Rank**	**D30-Rank**
Brand	7	3	1	6
G6	1	1	7	2
G3	4	2	6	4
G4	6	6	3	1
G7	2	4	5	7
G2	5	5	2	3
G5	3	7	4	5

Table 2 – 100 mg Rank Order

100 mg	Lamotrigine Tablets			
Code	**C-Rank**	**CU-Rank**	**AV-Rank**	**D30-Rank**
Brand	2	5	6	2
G1	8	8	3	11
G2A	5	6	1	10
G2B	10	3	8	5
G3	7	2	10	3
G4	1	1	7	8
G5A	3	4	9	6
G5B	6	7	5	7
G5C	9	10	2	9
G5D	4	9	4	4
G5E	11	11	11	1

Acknowledgement

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* EQUIGEN – Equivalence Among Antiepileptic Drug Generic and Brand Products in People with Epilepsy single-dose 6 period replicate design (EQUIGEN–Single-dose Study) and chronic-dosing double blind 4 period replicate design (EQUIGEN–Chronic Study).

Figure 2 – 25 mg Content Assay

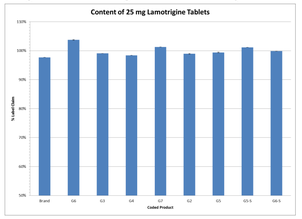


Figure 3 – 25 mg Content Uniformity

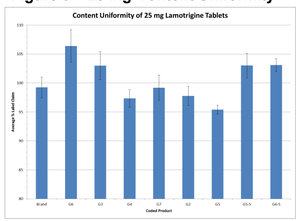


Figure 4 – 25 mg CU Acceptance Values

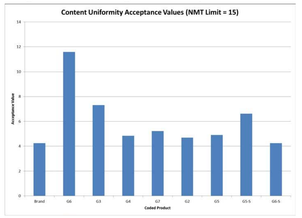
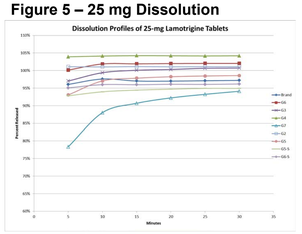


Figure 5 – 25 mg Dissolution



Results & Discussion

Content results (Figures 2 & 6) appear to show typical manufacturer-to-manufacturer variability. Impurities were extremely low or not detected in all lots; thus, not considered in the rankings. Content Uniformity results were evaluated by looking at both the average content uniformity (Figures 3 & 7) and the acceptance values (Figures 4 & 8). Dissolution (Figures 5 & 9) was rank ordered at each timepoint, but no significant changes were noted; thus the 30 minute ranking (D30) was used for comparison. A wide variation in the early dissolution timepoints was noted; however, clinical relevance of this was not believed to be significant based on the ANDA bioequivalence data. 100 mg products "G4-C" and "G5E-C" were selected for a chronic dose study. 25 mg products from manufacturers of "G6" and "G5" were selected for a single-dose study. The lots initially tested from these manufacturers were no longer available; thus, other lots from the same manufacturers ("G5-S" and "G6-S") were tested and used in the clinical program. Product "G7" was initially under consideration instead of "G5"; however, this product was discontinued by the manufacturer after testing was completed. Blinding of results is being maintained to protect the integrity of the clinical evaluation.

Conclusions

A method for selecting most disparate generics for a clinical investigation was developed based the sum of differences in rank order for results of *in vitro* testing. This approach combined with assessment of formulation composition and ANDA bioequivalence data was used to select products for use in the EQUIGEN clinical studies.

Affiliations

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Figure 6 – 100 mg Content Assay

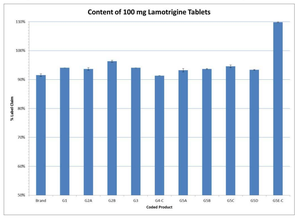

Figure 7 – 100 mg Content Uniformity

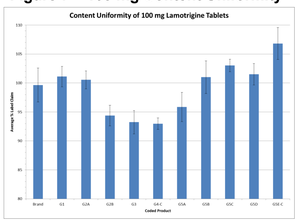

Figure 8 – 100 mg CU Acceptance Values

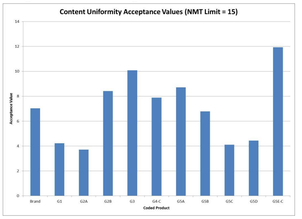

Figure 9 – 100 mg Dissolution