SUBJECT-UNRECOGNIZED MEDICATION ADHERENCE ERRORS IN THE EQUIVALENCE AMONG GENERIC AED (EQUIGEN) CHRONIC DOSE TRIAL

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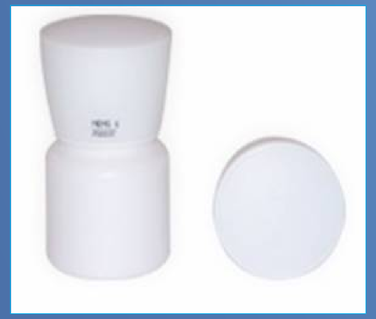
Rationale:

- Chronic-dose pharmacokinetic studies require a high level of subject medication regimen adherence.
- Incomplete adherence is one of the reasons the FDA favors single over chronic dose studies for bioequivalence testing.
- Strict adherence criteria were required in the EQUIGEN chronic-dose study
  - A 6-center, prospective, randomized, investigator-blinded, replicate, 4-period pharmacokinetic (PK) trial of chronic dosing of two, disparate, FDA-approved generic 100 mg lamotrigine products to determine the differences in PK parameters after generic-to-generic switching.
  - Dose 1, 2, 3, or 4 tablets q 12 hours
  - Each 2-week PK period concluded with a 12-hour PK session.
- We assessed medication regimen adherence in these highly compliant subjects.



Methods:

- Adherence to the study drug regimen (dosed every 12 hours) was assessed using:
  - Double tablet counts – by coordinator
    - Upon dispensing and return
    - Central pharmacy also performed tablet count prior to bottle shipment
    - All bottles had 128 tablets of 100 mg lamotrigine
  - Daily dose diaries
    - with dual alarm clock
  - Medication Event Monitoring System (MEMS) capped bottles.
- Adherence criteria required that during each period the subjects:
  - Period start to day minus 9 - miss no more than one dose
  - Days minus 8 to minus 4 - take entire daily dose
  - Days minus 3 to the PK day - take dose within one hour of dose time.

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Results:

- 33 subjects completed all 4 periods
  - 2 dropouts – not included
- 132 completed treatment periods with 3696 doses
- **8 (0.22%) dosing errors for which the subjects were unaware**:
  - 2 subjects unknowingly took an extra dose
    - MEMS cap opened twice at a dose time with tablet count in agreement with an extra dose taken.
  - 4 subjects unknowingly missed doses
    - Diaries had all doses recorded as taken
      - 3 subjects - MEMS cap not opened at a dose time
        - extra dose in bottle on tablet count
      - 1 subject - MEMS cap opened at all dose times
        - extra dose in bottle on tablet count.
  - 2 subjects had probable partial dose errors:
    - 1 subject - missing 1 tablet from bottle suggesting an extra tablet was taken with one dose (regimen: 2 tablets per dose)
    - 1 subject - 1 extra tablet in bottle suggesting that with one dose only 3 tablets were taken (regimen: 4 tablets per dose).

Conclusions:

- Rare, unrecognized dose errors are made by highly adherent patients.
- Slight dosing errors did not cause adverse effects or breakthrough seizures in patients.
- The use of MEMS caps and close follow-up increased adherence.