4. WORK PLAN AND METHODOLOGY

WORK PLAN FOR BIOEQUIVALENCE STUDY OF TOPIRAMATE

1. Literature Review

2. Fasting Bioequivalence Study
   - Clinical Phase
     - Preparation of Clinical study Protocol
     - Recruitment of Volunteers and Test Drug
     - Screening of volunteers
     - Conduction of clinical phase
   - Bioanalytical Phase
     - Procurement of Working/Reference Standards
     - Bioanalytical Method development for quantification of drug
     - Bioanalytical Method Validation
     - Conduction of Subject sample analysis of fasting study

3. Fed Bioequivalence Study
   - Clinical Phase
     - Preparation of Clinical study Protocol
     - Recruitment of Volunteers
     - Screening of volunteers
     - Conduction of clinical phase
   - Bioanalytical Phase
     - Conduction of Subject sample analysis of fed study

4. Statistical Phase
   - Statistical analysis of Fasting study
   - Statistical analysis of Fed study

5. Final Report Preparation

METHODOLOGY FOR BIOEQUIVALENCE STUDY OF TOPIRAMATE

| Study design | AN OPEN LABEL, PIVOTAL, RANDOMIZED, TWO-WAY CROSSOVER, |
**Background**

Topiramate is an antiepileptic (AED) agent indicated for Monotherapy epilepsy: initial monotherapy in patients $\geq 2$ years of age with partial onset or primary generalized tonic-clonic seizures. Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients $\geq 2$ years of age with seizures associated with Lennox-Gastaut syndrome (LGS). Migraine: Treatment for adults for prophylaxis of migrane headache.

**Study objectives**

- The primary objective of this study is to compare the rate and extent of absorption of Topiramate Tablets 25 mg of Alkem Laboratories Limited, with Topamax® Tablets (Topiramate Tablets 25 mg) of Ortho-McNeil Neurologics, Inc., USA in healthy adult male human subjects under fasting or fed conditions.
- The secondary objective is to monitor the safety of a single dose of Topiramate Tablets 25 mg in healthy adult male human subjects.

**Study Design**

Balanced, Open label, randomized, two treatment, two period, two sequence, single dose, cross over comparative oral bioavailability study in healthy, adult, human male subjects under fasting or fed conditions.

**Study Duration**

Duration of clinical phase will be 17 days including a wash out period of at least 14 days.

**Sample Size**

Sufficient number of subjects will be enrolled to dose at least 24 subjects.

**Investigational Drug Products**

<table>
<thead>
<tr>
<th></th>
<th>Test (T)</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td>Topiramate Tablets 25 mg of Alkem Laboratories Limited, India Each Tablet contains: 25 mg of Topiramate</td>
<td>Topamax® (Topiramate Tablets 25 mg) of Ortho-McNeil</td>
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### Ph D. Synopsis

<table>
<thead>
<tr>
<th>Screening</th>
<th>Neurologics, Inc., USA</th>
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<tr>
<td>Each Tablet contains: 25 mg of Topiramate</td>
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#### Screening

Demographic data, medical and medication history, physical examination, 12 lead ECG, vital signs, hematology, Biochemistry, HIV I & II, Hepatitis B & C, urine analysis and Chest X-ray PA view.

Drugs of abuse and breathe alcohol test will be performed before check in and each ambulatory samples in each period.

#### Confinement

In each period, the subjects will be housed from at least 12 hours before drug administration to 36 hours after drug administration. Again you will have to visit the clinical facility for the ambulatory samples (48.0, 72.0, 96.0 and 120.0 hrs post dose) of each period.

#### Drug Administration Procedure

In each period, after an overnight fast of at least 10 hours, subjects will receive a single dose of Test (T) or Reference (R) product while in sitting posture with about 240 ml of water at ambient temperature according to the randomization schedule. But in case of fed study, high fat and high calorie breakfast will be provided before dosing.

#### Study Restrictions

<table>
<thead>
<tr>
<th>Water</th>
<th>1.00 hour pre-dose to 1.00 hour post-dose (except the water given during dosing).</th>
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<tbody>
<tr>
<td>Physical Activity</td>
<td>Subjects must be in sitting/semi-inclined posture for the first 02 hours post dose.</td>
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<td>Food</td>
<td>Subjects will not be allowed to eat anything 10 hrs before and 4 hours after dosing. Further diet will be provided at appropriate times. But in case of fed study, high fat and high calorie breakfast will be provided before dosing.</td>
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#### PK Sampling

Total 18 samples will be collected from each subject per period at pre-dose (0.0) and 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0, 24.0, 36.0 (within + 2 minute of scheduled time) and 48.0, 72.0, 96.0 and 120.0 hrs post dose ambulatory samples (within + 2 hrs of scheduled time).

#### Total Blood Loss

Total 36 samples of 5 ml each (180 ml), 6.0 ml discarded blood, 14 ml blood for pre-study screening and 8 ml blood for post study test, amount to total blood loss.
<p>| <strong>Sample Collection</strong> | of approximately 208.0 ml. Samples will be collected through an indwelling I.V. cannula (vein flow) inserted in the forearm vein of the subject. If required, it may also be collected through a fresh vein puncture. 5ml of blood per sample will be collected using syringe and transferred to the pre-labeled heparinized sample collection tubes kept in the ice box. Blood samples will be collected after discarding the first 0.2 ml of heparinized blood from the venous cannula. Heparin in normal saline solution will be used to keep the indwelling cannula free from the blockade. |
| <strong>Plasma Separation</strong> | Blood samples will be centrifuged to separate plasma as soon as possible (within one hour after last blood sample collection of respective time point) if not possible store the samples in the -20°C±2°C till centrifuge. The samples will be centrifuged at 4000 rpm, between 8°C -10°C for 10 minutes. All plasma samples will be stored in interim storage at -20°C±2°C till all the samples were collected in each period. After completion of the study the plasma samples will be transferred to the Bioanalytical department and will be stored upright at -70°C or colder. |
| <strong>Bioanalytical Procedure</strong> | The concentration of Topiramate in plasma will be quantified using LC-MS/MS method according to the regulatory guidelines and in-house SOP’s. |
| <strong>Pharmacokinetic Parameters:</strong> | Employing the estimated Plasma concentration time profile of Topiramate following Pharmacokinetic parameters will be calculated Using SAS Statistical Software (9.1.3 or higher, SAS institute Inc., USA). Primary PK Parameters: $C_{\text{max}}, \text{AUC}<em>{0-t}$ and $\text{AUC}</em>{0-\infty}$ Secondary PK Parameters: $K_{\text{el}}, T_{\text{max}}$ and $T_{1/2}$. Descriptive statistics like minimum, maximum, mean, geometric mean, median, standard deviation and coefficient of variation for all pharmacokinetic parameters will be calculated. |
| <strong>Statistical Evaluation:</strong> | Summary statistics, ANOVA, intra subject variability, 90% confidence intervals and power will be calculated by non compartmental method using SAS® statistical |</p>
<table>
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<th><strong>Ph D. Synopsis</strong></th>
<th><strong>Software</strong> (9.1.3 or higher, SAS institute Inc., USA).</th>
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<td><strong>Statistical Evaluation:</strong></td>
<td>Bioequivalence between the Test and reference formulations will be assayed by the calculation of the 90% confidence Interval of test / reference ratio (Least Square Mean) for $C_{\text{max}}$, $\text{AUC}<em>{0-t}$ and $\text{AUC}</em>{0-\infty}$ based on Topiramate (after log transformation) for Topiramate.</td>
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<td><strong>Bioequivalence Criteria</strong></td>
<td>To be considered bioequivalent, T/R ratio &amp; the 90% confidence interval of the primary parameters should fall within the interval 80.00% to 125.00%. The power of the ANOVA to detect a 20% difference ($\alpha=0.05$) between formulations will be determined. 90% two one sided confidence interval for the difference of the means of the logarithmic transformed values of $C_{\text{max}}$, $\text{AUC}<em>{0-t}$ and $\text{AUC}</em>{0-\infty}$ at 5% level of significance is between 80.00% and 125.00% for Topiramate.</td>
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<td><strong>Safety Monitoring</strong></td>
<td>A physician or sub investigator will always be available during the study period. In each period, Blood pressure, Pulse rate, Oral temperature, Respiratory rate and well-being will be examined and questioned at the time of admission in to clinical unit, prior to drug administration (0.0 hr) and at 2.0, 4.0, 6.0, 4.0, 8.0, 12.0 and 24.0 hours post dose (within ± 45 minutes from the scheduled time) and at the time of check out and each ambulatory samples (48.0, 72.0, 96.0 and 120.0). Vital signs, CBC, S. Bilirubin, SGOT, SGPT, S. Alkaline Phosphatase, Blood urea nitrogen, S. Creatinine will be done at the end of the period-II and in case of withdrawal of the subject due to any reason. In house emergency care unit will be kept ready for any emergency and a consultant physician and emergency care hospital will be kept informed during the study period.</td>
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<td><strong>Ethical Issues</strong></td>
<td>The study will commence only after a written approval obtained from the Independent Ethics Committee. The study will be conducted as per the ICH Guidelines, ICMR guideline, USFDA guidance on BA/BE studies and in accordance with the declaration of Helsinki (2004, Japan), IEC approved protocol and in-house SOPs.</td>
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