2. LITERATURE REVIEW

1. **US National Institute of drugs et al., (2009)**\(^1\): Studied an open-label, randomized, single-dose, 2-way crossover, relative bioavailability study performed on 24 healthy adult male volunteers and 4 alternates. All 28 subjects completed the clinical phase of the study. In each period, subjects were housed from the evening before dosing until after the 24-hour blood draw. Subjects were to return for the 48-, 72-, 96- and 120-hour blood draws. Both periods were separated by a washout period of 14 days.

2. **Ritesh Singla et al., (2011)**\(^2\): Evaluated the acute ocular side effects of Topiramate in patients of migraine. Retrospective study done. Topiramate which is recently being used quite frequently and effectively in the treatment of migraine has rare but potential side effects in the form of bilateral acute angle closure glaucoma which can be effectively managed with prompt stoppage of Topiramate therapy and conservative management.


4. **Luca Spaccapelo et al., (2011)**\(^4\): Studied on Topiramate-associated acute glaucoma in a migraine patient receiving concomitant citalopram therapy: a case-report. A 34 year-old man with diagnosis of migraine with and without aura that developed myopia and acute glaucoma after 7 days of treatment with topiramate. The patient had also been taking citalopram daily for two months. Both topiramate and citalopram have been related to the increase of intraocular pressure and the development of glaucoma.

5. **US National Institute of drugs et al., (2011)**\(^5\): Conducted Topiramate Bioequivalence Study Brazil – Fast. This study is prospective, open-label, randomized, crossover, single dose, with 02 treatments, 02 sequences and 02 periods. The volunteers received, in each period, the reference or the test formulation, according to the randomization list, under fasting conditions, in order to evaluate if the reference and test formulations are bioequivalent.

6. **Ipharma SA de CV et al., (PMID 19302913)**\(^6\): Conducted Bioequivalence of single 100-mg doses of two oral formulations of topiramate: an open-label, randomized-sequence, two-period crossover study in healthy adult male Mexican volunteers. The proprietary form of topiramate is indicated in Mexico as an antiepileptic agent and in the prophylaxis of migraine headaches. However, before generic topiramate is placed on the market, pharmacokinetic studies investigating the bioequivalence of generic and branded formulations are needed. This study did not find any statistically significant differences in C(max) or AUC values between the test and reference formulations of oral topiramate.
100 mg in this population of healthy adult male Mexican volunteers. On that basis, and according to both the rate and extent of absorption, the test and reference formulations met the regulatory criteria for bioequivalence. Both formulations were well tolerated.

7. **FDA Approved Labeling Text et al (2011)**: Evaluation of TOPAMAX® is a prescription medicine used: to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in adults and children 2 years and older, with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older, to prevent migraine headaches in adults.

8. **Guerrini R, Parmeggiani L et al (2011)**: Studied on “Topiramate and its clinical applications in epilepsy”, Expert Opin Pharmacother (2006);7: pp. 811–823. Topiramate, an AED with multiple putative mechanisms of action, has proven to be remarkably effective through a wide series of trials in several types of epilepsy. Slow titration of TPM to a low-medium dosage will enhance tolerability. Good efficacy with an excellent tolerability and safety profile are obtained at doses (200mg/day in adults and ~3.5mg/kg/day in children. Furthermore, long-term follow-up studies indicate that the response to TPM is maintained.

9. **Saavedra I, Tamayo E, Gamboa A, et al., (PMID 20420791)**: Studied on Relative bioavailability study with two oral formulations of topiramate using a validated UPLC-MS/MS method. Changes in bioavailability of anticonvulsant drugs such as topiramate may cause loss of or worsened seizure control. Thus, the purpose of this study was to evaluate, in a double-blind crossover design, the bioavailability between two oral formulations of topiramate in healthy volunteers after a single dose. The protocol, approved by the Institutional Committee of Ethics, consisted of administration of 1 tablet of 100 mg of topiramate of each formulation (Toprel and Topamax), to 20 healthy volunteers after a 12 h overnight fast, using an open, two-period, randomized, crossover and double-blind design. Thus, the plasma concentrations (Cp) of topiramate were measured at predetermined intervals of time, from 0 to 24 h, using a validated UPLC-MS/MS method. Based on plasma concentration-time profiles we obtained the pharmacokinetic parameters.

10. **Jin-Hee Park, Yoo-Sin Park, et al., (2008)**: Determined plasma topiramate concentration using LC-MS/MS for pharmacokinetic and bioequivalence studies in healthy Korean volunteers. A rapid, simple and validated liquid chromatography coupled to tandem mass spectrometric method (LC-MS/MS) for topiramate analysis in human plasma has been applied to pharmacokinetic and bioequivalence studies in 24 healthy male Korean volunteers. The procedure involves a simple liquid extraction of topiramate and prednisone (internal standard) with acetonitrile and separation by HPLC equipped with a Capcell Pak C18 column using acetonitrile-0.1% triethylamine (80:20, v/v) as a
mobile phase. Detection was carried out on an API 2000 MS system by multiple reactions monitoring mode.

11. **A.R. Towne, MD; L.K. Garnett, RN, et al., (2003)**: The use of topiramate in refractory status epilepticus. In cases of refractory status epilepticus (RSE) unresponsive to sequential trials of multiple agents, a suspension of topiramate administered via nasogastric tube was effective in aborting RSE, including one patient in a prolonged pentobarbital coma. Effective dosages ranged from 300 to 1,600 mg/d. Except for lethargy, no adverse events were reported.

12. **ALI MOHAMMADI et al., (2010)**: Developed a Stability-Indicating High Performance Liquid Chromatographic Method for the Analysis of Topiramate and Dissolution Rate Testing in Topiramate Tablets, A stability-indicating high performance liquid chromatographic (HPLC) method was developed and validated for the quantitation and dissolution determination of topiramate in tablet dosage forms. An isocratic separation was achieved using a phenyl column with a flow rate of 1 mL/min using UV detection at 264 nm. Topiramate has low UV absorbivity and was subjected to derivatization with 9-fluorenylmethyl chloroformate (FMOC-Cl). The mobile phase for the separation consisted of acetonitrile: 50 mM sodium dihydrogen phosphate (NaH2PO4) containing 3% v/v triethylamine (pH 2.8) in a 48:52 v/v ratio.

13. **Gh. Bahrami, ALI MOHAMMADI et al., (2004)**: Developed Sensitive analytical method for Topiramate in human serum by HPLC with pre-column fluorescent derivatization and its application in human pharmacokinetic studies. A sensitive and specific high performance liquid chromatographic method for quantitation of topiramate in human serum was developed using HPLC with fluorescence labeling reagent. Topiramate was extracted from human serum by dichloromethane and derivatized by reaction with 9-fluorenylmethyl chloroformate (FMOC-Cl) in the presence of borate buffer.

14. **Sandra D Gawley et al., (2009)**: Studied on Topiramate induced acute transient myopia: a case report, Topiramate is a sulfamate-substituted monosaccharide mainly used to treat epilepsy in children and adults and for prophylaxis of migraine. This article describes a case of topiramate induced acute transient myopia. The underlying mechanism and management is discussed.

15. **US National Institute of drugs et al., (2008)**: Investigated the bioequivalence of Mylan's topiramate sprinkle 25 mg capsule to Ortho-McNeil's Topamax® Sprinkle 25 mg capsule following a single, oral 25 mg (1 x 25 mg) dose sprinkled on one teaspoon of applesauce under fasting conditions.

16. **Pediatric Neurology et al., (1999)**: Studied on topiramate pharmacokinetics and tolerability in children with epilepsy, The pharmacokinetic and safety profile of topiramate as adjunctive therapy was assessed in pediatric patients with epilepsy in an open-label, 4-week, single-center study. Six children from each of the following age groups were enrolled: 4-7 years, 8-11 years, and 12-17 years.
Patients received topiramate 1 mg/kg/day for 1 week, with subsequent progressive weekly increases in dosage to 3, 6, and then 9 mg/kg/day or 800 mg/day, whichever was less.

17. **Teva Pharmaceuticals USA, et al., (2009)**: Studied to compare the rate and extent of absorption of topiramate 25 mg capsules (test) versus Topamax (reference) administered as 2 x 25 mg capsules under fasting conditions. Randomized, 2-Way Crossover, bioequivalence Study of Topiramate 25 mg Capsules and Topamax 25 mg Sprinkle Capsules Administered as 2 x 25 mg Capsules in Healthy Subjects Under Fasting Conditions.

18. **Clinical Pharmacokinetics, et al., (2009)**: Evaluated Pharmacokinetic Interactions of Topiramate. Topiramate is a new antiepileptic drug (AED) that has been approved worldwide (in more than 80 countries) for the treatment of various kinds of epilepsy. It is currently being evaluated for its effect in various neurological and psychiatric disorders.

19. **Rx drug information, pharmaceutical research, et al., (2009)**: Studied on Controlled-Release Phentermine /Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. A double-blind randomized controlled trial to study the efficacy of topiramate in a civilian sample of PTSD.

20. **Pill Identifier Search et al., (2011)**: Determined precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

21. **Suhas Sahebrao Khandave Search et al., (2010)**: Evaluated Performance of the Truncated Area Under Curve (AUC) as a Primary Pharmacokinetic Parameter in Bioequivalence Studies. Prolonged pharmacokinetic sampling is a challenge for successful conduction of the bioequivalence studies for drugs having long elimination half-lives. The regulatory authorities have recommended an alternative to consider the partial AUC (AUC0-72) for studying bioequivalence. However, the results obtained from such truncated approach are not consistent and needs further exploration. We have investigated the suitability of truncated AUC in the field of bioequivalence.

Film-Coated Tablets to Caduceus Pharma Limited (PL 24668/0007-14) on 13th March 2008. The products are prescription-only medicines.

23. **Guidance on Topiramate, et al., (2009)**: Analyzed to measure (in appropriate biological fluid) Topiramate in plasma. Bioequivalence based on (90% CI): TopiramateWaiver request of in-vivo testing: 15 mg based on (i) acceptable bioequivalence studies on the 25 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Waiver request of in-vivo testing: 15 mg based on (i) acceptable bioequivalence studies on the 25 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

24. **Delbelo MP, et al., (2005)**: Studied on a pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. Topiramate was well tolerated; however, the results are inconclusive because of premature termination resulting in a limited sample size. Adequately powered controlled trials are necessary to determine whether topiramate has efficacy in reducing symptoms of acute mania in children and adolescents.

25. **Emma Varkey et al.,(2011)**: Studied on the migraine prophylaxis: A randomized study using relaxation and topiramate as controls. Study aimed to evaluate the effects of exercise in migraine prevention. Concluded that Exercise may be an option for the prophylactic treatment of migraine in patients who do not benefit from or do not want to take daily medication.

26. **Shang-Peng Wu et al., (1998)**: Studied on Frequency-dependent inhibition of neuronal activity by topiramate in rat hippocampal slices. The major findings of this study are: (1) topiramate reduced the slope of fEPSP and the amplitude of PS in a frequency- and concentration-dependent manner; (2) topiramate reduced the amplitude of pharmacologically isolated presynaptic fiber volley without affecting the ratio of paired-pulse facilitation; (3) topiramate affect neither paired-pulse inhibition nor GABAergic-mediated IPSP; (4) topiramate reduced the total number of action potentials evoked by a depolarizing current pulse; and (5) topiramate suppressed the the bicuculline-induced PDS.

27. **Tobias Leniger et al., (2004)**: Studied on Topiramate modulates pH of hippocampal CA3 neurons by combined effects on carbonic anhydrase and Cl-/HCO3 _- exchange. TPM reduced the steadystate pH of CA3 neurons in slices. This effect was most likely due to lowered HCO3 concentration inside cells and was caused not only by a decreased carbonic anhydrase activity but also by an augmentation of Na+-independent Cl/HCO3 exchange. The resulting decrease of pH was sufficient to explain the suppressive effects of TPM in the 4-AP epileptic model system. In line with this hypothesis, TPM-induced changes of epileptiform activity could be reversed by an alkalosis.

29. Diana Ferraro et al., (2008) 29: Reviewed Topiramate in the prevention of pediatric migraine. A total of five papers were reviewed: two randomized controlled trials (RCTs), a posthoc subset analysis of adolescents who had been included in three RCTs carried out on adults and two open studies. Topiramate has been proven to reduce headache frequency and the accompanying disability.

30. Y. L. Lo et al., (2010) 30: Studied pilot of topiramate dosages for migraine prophylaxis in an Asian population. Topiramate is known to be efficacious in migraine prophylaxis, but its optimal dose has not been systematically studied in the Asian population. Here, we show that a fixed low dose of topiramate 25 mg/day is efficacious in migraine prophylaxis and also attest to advantages in terms of medication cost savings and more favourable side effect profile.


32. Martin Holtkamp et al., (2005) 32: Reviewed Erectile Dysfunction with Topiramate. The two current cases indicate that erectile dysfunction should be considered as part of the spectrum of reversible adverse events in patients treated with TPM.

33. Stephen D et al., (2007) 33: Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. This was a randomized, placebo-controlled, parallel-group, multicenter study consisting of 16 weeks of double-blind treatment. Subjects aged 18 to 65 years with 15 or more headache days per month, at least half.

34. Marie-Aude Rigoulot et al., (2003) 34: Reviewed on Effects of Topiramate in Two Models of Genetically Determined Generalized Epilepsy, the GAERS and the Audiogenic Wistar AS. These results support the broad spectrum of antiepileptic activity of TPM, confirming its efficacy in primary generalized seizures of both tonic–clonic and of the absence type.

35. Graeme J. Sills et al., (2003) 35: Reviewed Vigabatrin, but not Gabapentin or Topiramate, Produces Concentration-related Effects on Enzymes and Intermediates of the GABA Shunt in Rat Brain and Retina. VGB treatment produced a significant (p < 0.05) dose-related increase in GABA concentrations and decrease in GABA-transaminase activity in all tissues investigated. This effect was most pronounced in the retina, where VGB concentrations were 18.5-fold higher than those in brain. In contrast, GBP and TPM were without effect on any of the neurochemical parameters investigated and did not accumulate appreciably in the retina.
36. M. Scott Perry et al., (2006): Experimented on Topiramate Loading for Refractory Status Epilepticus in Children. Patients with SE refractory to therapeutic doses of at least two antiepileptic medications were given TPM, 10 mg/kg/d, for 2 consecutive days, followed by maintenance doses of 5 mg/kg/d. Experience indicates that TPM loading can be effective in the treatment of RSE in children.

37. J. Pascual et al., (2006): Tested the combination beta-blocker plus topiramate in refractory migraine. Combining a beta-blocker plus topiramate showed benefit in around 60% of those patients who had not responded to the treatment in monotherapy. Even though onotherapy remains the rule in migraine prevention.

38. Jung-Mi Kim et al., (2009): Studied on Long-term Effectiveness and tolerability of Topiramate in Children with Epilepsy under the Age of 2 Years: 4-Year Follow-up. This is a long-term, open label, observational study aimed to broaden our clinical experiences in managing infants and toddlers with epilepsy. Studies showed that TPM has a broad spectrum of antiepileptic effects without any potentially dangerous side effects in children (6, 11-16).

39. Marco Mula et al., (2006): Psychopharmacology of Topiramate from epilepsy to bipolar disorder, Topiramate (TPM) is one of the novel antiepileptic drugs and exhibits a wide range of mechanisms of action. Efficacy of TPM has been demonstrated in partial-onset seizures and primary generalized seizures in adults and children, as both monotherapy and adjunctive therapy. TPM has been proposed as an add-on treatment for patients with lithium resistant bipolar disorder, especially those displaying rapid-cycling and mixed states. This paper reviews the multiple mechanisms of action and the tolerability profile of TPM in the light of its therapeutic potential in affective disorders.

40. Bankole A. Johnson et al., (2007): Studied on kinetic and cardiovascular effects of acute Topiramate dosing among non-treatment seeking, methamphetamine-dependent individuals. The administration of topiramate and methamphetamine under controlled conditions in the human laboratory was safe. There were no hemodynamic interactions between topiramate and methamphetamine. Although there was no significant kinetic interaction between Topiramate and methamphetamine, there was a trend for topiramate to increase plasma methamphetamine level.

41. Susan L. McElroy et al., (2000): Studied on Open-Label Adjunctive Topiramate in the Treatment of Bipolar Disorders. These preliminary open observations of adjunctive topiramate treatment suggest that it may have antimanic or anticycling effects in some patients with bipolar disorder, and may be associated with appetite suppression and weight loss that is often viewed as beneficial by the patient and clinician. Controlled studies of topiramate’s acute and long-term efficacy and side effects in bipolar disorder appear warranted.