1.0 INTRODUCTION

Epilepsy is a chronic condition characterized by recurrent unprovoked epileptic seizures that may be accompanied by a constellation of neurologic conditions and comorbidities. A disease like epilepsy, if not adequately controlled, can result in significant morbidity, mortality, and financial burden to the health care system.

As per World Health Organization estimates, epilepsy affects nearly 50 million people worldwide. It has been estimated that India with 6–10 million persons with epilepsy accounts for nearly 1/5th of the global burden of epilepsy. A study done in Indian population calculated that the total cost per epilepsy case was US$ 344 per year (or 88% of the average income per capita) and was equivalent to 0.5% of gross national product (Thomas et al, 2001).

Epilepsy is a persistent condition with associated consequences beyond that of the seizure (World Health Organization, 2006). Optimal pharmacologic treatment of a persistent and disabling neurologic condition like epilepsy requires that stable and appropriate concentrations of antiepileptic drugs (AEDs) be maintained over extended periods of time (Leppik and Hovinga, 2013).

Many antiepileptic drugs (AEDs) have short half-lives with large fluctuations in peak-to-trough plasma concentrations. Consequences of these pharmacokinetic (PK) properties may include adverse events (AEs) and breakthrough seizures, potentially leading to poor adherence. To address these challenges, newer formulations of these AEDs have been developed using unique extended-release (ER) technologies. These technologies extend the dosing interval such that dosing frequency can be minimized, which may improve patient adherence (Leppik and Hovinga, 2013). Conceptually, the stable plasma concentration profile of extended release AED formulations is expected to minimize peak concentration–related adverse events and improve compliance and seizure control (Radtke, 2001 and Sommerville, 2006). Extended release formulations may contribute to better tolerability and improved efficacy (Radtke, 2001). In so doing, tolerability advantages may lead to increased AED effectiveness by improving adherence and allowing higher doses if clinically indicated. Direct PK comparison studies of IR and ER formulations have found that most ER formulations have a lower fluctuation index ([Cmax–Cmin]/Cavg) compared with the IR versions. (Leppik and Hovinga, 2013).

Several, but not all broad-spectrum AEDs are now available in formulations modified to allow once-daily dosing. These extended-release (ER) formulations leverage the efficacy of the immediate-
release (IR) compound while attempting to improve other parameters such as tolerability and convenience. Inherent characteristics of the original molecule (e.g., bioavailability, solubility, permeability), along with the wide variety of ER technologies that modulate these characteristics, result in great variability in the extent to which available ER formulations improve the pharmacokinetics (PK) and pharmacodynamics (PD) of an agent (Leppik and Hovinga, 2013).

Assessment of adherence should be a routine part of management of epilepsy (Jones et al, 2006). Current estimates of non-adherence in epilepsy are similar to those in other chronic illnesses and range from 30 to 50%. Poor adherence may be the most important cause of poorly controlled epilepsy (Gomes et al, 1998).

Noncompliance is a major factor in suboptimal control of epileptic seizures and is a serious hindrance to successful treatment of patients with epilepsy. It can result in increased healthcare costs and put both the patients and others around them at unnecessary risk (Leppik, 1990). Noncompliance negates the usefulness of the advances made in the diagnosis and treatment of epilepsy and is perhaps the single most important factor in increasing the costs of care for people with epilepsy.

The overarching goal in epilepsy treatment is complete long-term seizure control with no or tolerable side effects. However, suboptimal adherence, which is common among individuals treated for epilepsy contributes to the challenge of achieving this goal (Manjunath et al, 2009). A retrospective analysis of an insurance claims database of >40 million patients showed that approximately 40% of patients using AEDs did not adhere to the prescribed drug regimen (Davis et al., 2008). The rate of nonadherence, defined as a medication possession ratio of <80%, ranged from 32–53% depending on AED and increased with age. Another study using this same database observed declines in adherence from the time of initiation of the first AED regimen through 12 months of follow-up, with adherence dropping to <50% (Manjunath et al, 2009).

At least 50% of patients with epilepsy have partial seizures. About 30%–70% of partial seizures are controllable with antiepileptic drugs (AEDs). The majority of these patients will need lifelong AED therapy. Strict AED compliance is often related to better tolerability and is a key factor in achieving better seizure control. An inverse relationship between the number of daily doses and compliance has been reported. Every increase in dosing frequency (from one to four doses per day) resulted in progressively worsening compliance and increased missed doses (Cramer et al, 1995, 2002 and Bialer, 2007).
Levetiracetam is a second-generation antiepileptic drug (AED) with a unique chemical structure and mechanism of action. Levetiracetam’s mode of action is not fully elucidated, but it has been found to target high-voltage, N-type calcium channels as well as the synaptic vesicle protein 2A (SV2A) (Carol et al, 2009).

Levetiracetam has nearly ideal pharmacokinetics. It is rapidly and almost completely absorbed after oral ingestion, is 10% protein-bound, demonstrates linear kinetics, is minimally metabolized through a pathway independent of the cytochrome P450 system, has no significant drug–drug interactions, and has a wide therapeutic index (Carol et al, 2009).

The immediate release (IR) formulation of Levetiracetam has been in the market since 2000. Extended release (XR) formulation of Levetiracetam (LEV) is approved by the Food and Drug Administration as an add-on to other antiepileptic drugs (AEDs) for adults with partial onset seizures. This is based on class-I evidence demonstrating significant seizure reduction in once daily dosing. Extended release (XR) formulation of Levetiracetam is marketed with the brand name of Keppra XR by UCB Pharma since 2008.

LEV-IR is proven effective as adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures and myoclonic seizures. It was shown to be equivalent to carbamazepine as first-line treatment for partial-onset seizures. The extended release formulation added advantages such as better tolerance and increased compliance (Sonmezturk and Azar, 2011).

Extended release Levetiracetam (LEV-XR) was developed to provide patients with the convenience of once-daily dosing, potentially improving compliance and the efficacy–tolerability ratio. It is shown that the pharmacokinetic profile for LEV-XR is comparable to immediate release Levetiracetam (LEV-IR) [Radtke, 2001 and Rouits et al, 2009]. While both LEV-XR and LEV-IR formulations may cause similar side effects that are generally well-tolerated, LEV-XR is usually preferred for its ease of use and more stable serum drug levels, both increasing patient compliance. The ease of conversion between LEV formulations also makes LEV-XR an attractive option (Ulloa et al, 2009).

Levetiracetam 1000 mg extended release tablet allows for once-daily dosing, which may increase compliance and, given the relatively constant plasma concentrations, may minimize concentration-related adverse effects. The most common reported adverse events with levetiracetam XR are somnolence, irritability, dizziness, nausea, influenza, and nasopharyngitis. Thus, Levetiracetam XR
provides an efficacious and well-tolerated treatment option for adjunctive therapy in the treatment of partial-onset seizures in patients’ ≥16 years of age (Prescribing information on Keppra XR™, 2012).

An extended release Levetiracetam 1000 mg formulation provides extended therapeutically effective plasma levels over a twenty-four hour period with diminished incidences of neuropsychiatric adverse events by eliminating the troughs and peaks of drug concentration in a patient’s blood plasma. The extended release Levetiracetam 1000 mg formulation also helps in improvement in patient compliance by reducing the dosing frequency to once daily.

Therefore, the present study was designed to assess the pharmacokinetics and bioequivalence of a new extended release tablet formulation, containing 1000 mg of levetiracetam, developed by Ranbaxy Laboratories Limited, India in comparison with two Keppra™ tablets 500 mg (immediate release formulation), administered twelve hourly, (each containing levetiracetam 500 mg) of UCB Pharma, Inc USA (Innovator Company). The present study was undertaken after taking approval from the JHIRB (Jamia Hamdard Institutional Review Board) on 22 April 2010.

OBJECTIVE:

The objective of the present study was to compare pharmacokinetic profile of a single oral dose of Levetiracetam 1000 mg extended release tablet manufactured by Ranbaxy Laboratories Limited with two oral doses of a Keppra™ 500 mg tablet (each tablet containing Levetiracetam 500 mg) of UCB Pharma Inc., administered twelve hourly, in healthy, adult, male, human subjects under fed condition.