Chapter 1: 

Introduction and Objectives

1.1 Introduction

1.2 Objectives
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Epilepsy is an oldest neurological disorder known to mankind, that affects people in every country throughout the world. Epilepsy knows no geographical, racial or social boundaries (Massimo A, et al., 1990). It occurs in men and women and can occur at any age, but is most frequently diagnosed in infancy, childhood, adolescence and old age. Anyone can be affected by seizures. In fact, up to 5% of the world’s population may have single seizure at some time in their lives, but a diagnosis of epilepsy is reserved for those who have recurring seizures, at least two provoked ones. 25 to 40 percent of patients with epilepsy continue to have seizures despite optimal treatment with traditional antiepileptic drugs. Treatment with standard anticonvulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital are often complicated by adverse effects and by failure to adequately control the seizures. Up to 61% of patients with seizures report having adverse effects with antiepileptic drugs. A need for development of new antiepileptic drugs with lower incidence of adverse effects has always been felt. Some new second generation antiepileptic drugs like levetiracetam, topiramate, zonisamide, lamotrigine, gabapentin, oxcarbazepine and tiagabine have been developed, which are similar in efficacy profile to the older agents but superior in adverse effects profile. Among these drugs lamotrigine is a broad spectrum antiepileptic drug used as adjunctive therapy or monotherapy in adults with partial seizures with or without secondary generalization (Goa KL, et al., 1993).

Results of pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage gated sodium channels. It produces a use and voltage-dependent block of sustained repetitive firing in neurons and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as glutamate-evoked bursts of action potentials (Goa KL, et al., 1993).

Lamotrigine is rapidly and completely absorbed from the intestine with no significant first pass metabolism. Peak plasma concentrations occur at 2.5 ± 1.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. Cmax (0.58 to 4.63 µg/mL) and AUC (29.9 to 211.9 mg*h/L) increase proportionately with dose. The pharmacokinetics is linear up to a dose of 450mg and binding to plasma proteins is about 55%. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronides in urine. Only about 2% of drug-related material is excreted in feces. The mean

Extensive experience with lamotrigine has indicated that it may be effective when other anticonvulsant drugs have failed. Clinical studies revealed that, it is effective for all kinds of epilepsy and used as monotherapy for partial epilepsy and as an add-on therapy in generalized epilepsy. It is a valuable broad-spectrum drug that is well tolerated but has few neurological adverse effects and skin rash. These adverse effects sometime limit the use of lamotrigine in some patients. Acute and chronic studies in humans have suggested that lamotrigine levels of 1-3 μg/mL are effective in controlling seizures. With rapid dose escalation even a single daily dose of lamotrigine achieves very high peak concentration in plasma, which causes the adverse effects (Frank MC, et al., 2000). Neurological adverse effects i.e. dizziness, headache, diplopia, ataxia, blurred vision and somnolence are normally seen at higher plasma concentrations, which are most likely to occur at peak plasma concentrations. Betts T, et. al. reported that, during the first 18 weeks of lamotrigine treatment 16.7% of patients reported nausea and vomiting at a mean concentration of 6.00 to 7.99 μg/mL and 100% reporting headache and ataxia at >10μg/mL (Betts T, et al., 1991). Similarly, Binnie CD, et al., reported adverse effects only in patients with levels above 3μg/mL (Binnie CD, et al., 1987). Hirsch LJ, et al. have identified a clear relation between lamotrigine serum concentrations and tolerability in patients with epilepsy (P < 0.0001). With levels less than 5.0 μg/mL, 7% of patients reported toxicity; with levels of 5 to 10 μg/mL, 14%; with 10 to 15 μg/mL, 24%; with 15 to 20 μg/mL, 34%; and with more than 20 μg/mL, 59%. The correlation between blood levels and tolerability was independent of concurrent medication. Increasing efficacy, as measured by seizure freedom for a 6-month period, occurred up to levels 20 μg/mL (Hirsch LJ, et al. 2004). A drug serum level is an important factor for identifying noncompliance; in addition, a baseline level is quite helpful as an internal reference for the patient (Neels HM, et al., 2004). Serum levels are particularly important for a drug like lamotrigine, whose clearance is increased by oral contraceptives by pregnancy and by enzyme-inducing drugs and decreased by valproate as well as other enzyme-inhibiting agents (Adab N, 2006).

Serious skin reactions including Steven Johnson Syndrome and toxic epidermal necrolysis occurring in patients taking lamotrigine was highlighted by the Committee of Safety of Medicine (CSM) in 1997 and has subsequently been discussed in the literature. The incidence of rashes associated with lamotrigine was initially estimated at approximately 0.8% in pediatric patients (aged 16 years or younger) (Anon, 1997, Mitchell P, 1997 and Anon, 1998) and 0.3% in adults, when used as adjunctive
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therapy for patients with epilepsy (Andres MK, 2005). Rash, which has occurred in 10% of patients in placebo-controlled trials has led to discontinuation of therapy in 1% of patients (most common cause of discontinuation). Skin reactions such as Stevens Johnson Syndrome are potentially fatal and have an incidence of 1 in 1000 person-years in adults. The incidence is higher in children. Valproate reduces the hepatic clearance of lamotrigine thereby increasing plasma concentrations of the drug by approximately two fold for a given dose. Studies suggested that rapid dose escalation of lamotrigine, even a single higher dose, could expose to an unacceptable risk of Stevens Johnson syndrome, particularly in patients taking valproate (Sladden M, 2004). Risk factors for skin reactions include high plasma concentration, concomitant sodium valproate therapy (Kocak S, et al., 2007), a high initial dose of lamotrigine and rapid dose escalation (Giuseppe F, et al., 2005 and Yalcin B, et al., 2000).

There is some evidence that, slow dosage escalation when initiating therapy may lessen the likelihood of development of severe rash (Sladden M, et al., 2004). Thus, dose reduction and slow dosage escalation are the techniques used to overcome peak concentration related adverse effects reported with lamotrigine (Frank MC, et al., 2000). Another technique, which can successfully reduce these adverse effects, would be the use of a sustained release formulation of lamotrigine. Sustained release formulation would produce a smaller Cmax. It will also maintain the steady state concentration with little fluctuations. It is thus, expected to reduce the incidence of neurological adverse effects i.e. dizziness, headache, diplopia, ataxia, blurred vision and somnolence, consequently expected to improve the compliance also.

1.2 Objectives

Lamotrigine sustained release formulation was developed with aim to maintain an effective plasma concentrations for the dosing interval, producing a lower but effective Cmax and smaller inter dose fluctuation of plasma concentration so as to,

1) lessen peak plasma concentration related adverse effects
2) effectively obviate the need for giving the drug in divided doses,
3) improve the quality of life and compliance in patients.

The present development of various strengths of sustained release formulation of lamotrigine is in consonance with the above objectives.