2.0 LITERATURE REVIEW

2.1 Medication compliance

Medication compliance can be defined as the extent to which the patient follows mutually agreeable instructions, or the extent to which actual drug taking behavior matches the prescribed regimen (Cramer et al, 2002).

2.2 Adherence to treatment in patients with epilepsy: Associations with seizure control and illness beliefs

Epilepsy has a prevalence of between 4 and 10 per 1000 population (Anderson et al, 1986) and is associated with physical, psychological and social problems (Devinsky, 1997). People with epilepsy have a higher rate of suicide, anxiety, depression, sudden unexplained death and accidental death (Garnett, 2000 and Leestma et al, 1984). Prolonged seizures may cause physical injury, neuronal death leading to cognitive impairment, and can be fatal (Leestma et al, 1984).

When treating an individual with epilepsy, there are factors that cannot be modified such as the age of onset, the aetiology of the seizures and the location of the epileptogenic zone. There are also some factors that may be amenable to an intervention to improve outcome. An obvious consideration for the clinician is the choice of medication to prescribe. Despite medication, it has been found that seizures persist in 20—35% of cases (Devinsky, 1999). It is necessary therefore to identify other “modifiable factors” which could lead to improved seizure control if targeted effectively.

Non-adherence to medication is widespread in chronic disease and is a major problem facing medical practice (Eraker et al, 1984). Current estimates of non-adherence in epilepsy are similar to those in other chronic illnesses and range from 30 to 50% (Leppik, 1990). This reduces the benefit that could be gained from the medication (Eraker et al, 1984; Dunbar-Jacob and Mortimer-Stephens, 2001). Poor adherence may be the most important cause of poorly controlled epilepsy (Gomes et al, 1998). Stanaway et al. found that 31% of seizures were precipitated by non-adherence to medication (Stanaway et al, 1985). If modifiable factors associated with non-adherence are understood, then it may be possible to intervene to improve adherence and therefore reduce morbidity caused by recurrent seizures.
2.3 Correlation between patient compliance and frequency of dosing in chronic disorders like Epilepsy

Improved Compliance:

- Epilepsy is a chronic disorder in nature and requires long-term therapy.

- Researches using electronic dosing monitoring to assess compliance have shown that approximately 75% of the doses are taken as prescribed, irrespective of the condition being treated or its severity (Straka et al, 1997). The rate of noncompliance with the pharmacological therapy in epilepsy has been reported to range from 30-50% (Leppik, 1990).

- Simplicity of treatment regimen in chronic illness, such as epilepsy, is very important. Primary goal of therapy in epilepsy is control of seizures and it has been reported that poor compliance in terms of the number and timing of doses and poor persistence with respect to long-term compliance often result in breakthrough seizures. (Cramer et al, 2002).

- Regimen complexity is an important determinant of non-compliance (Cramer et al, 2002). Erratic compliance or non-compliance often leads to discontinuation of therapy and it increases with
  - Increase in frequency of dosing
  - Increase in number of drugs patient is taking

- Inadequate compliance results in poor outcome, despite the best efforts of the medical team (Cramer et al, 2002).

- Compliance or dose taking is inversely related to frequency of to the prescribed number of doses per day. Various studies have shown that maximum compliance is achieved with once daily dosing regimens (Table 1). (Claxton et al, 2001; Cramer et al, 1989; and Eisen et al, 1990).
Table 1. Patient Compliance and frequency of Dosing

<table>
<thead>
<tr>
<th>Prescribed Daily Dosing Frequency</th>
<th>Compliance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once Daily</td>
<td>79±14</td>
</tr>
<tr>
<td>Twice Daily</td>
<td>69±15</td>
</tr>
<tr>
<td>Thrice Daily</td>
<td>65±16</td>
</tr>
<tr>
<td>Four times a Day</td>
<td>51±20</td>
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Improved Efficacy and Safety:

- By controlling the rate of drug release, and hence absorption, extended release preparations aim to provide close to constant concentrations over a prolonged period of time.

2.4 Extended-release formulations of antiepileptic drugs and the rationale for their development

Extended-release products are designed to prolong the absorption of drugs with short half-lives, thereby allowing longer dosing intervals while minimizing fluctuations in serum drug levels.

The relationship between serum drug concentration and clinical effects of antiepileptic drugs (AEDs) can be complex and reducing fluctuations in serum drug levels is not equally advantageous for all AEDs. Extended-release formulations have been shown to be particularly valuable for Carbamazepine, whereas for other AEDs advantages, other than prolongation of the dosing interval, have not been clearly demonstrated.

Differences in bioavailability may exist between extended-release and immediate-release formulations and among different brands of extended-release products. Therefore, when switching from one formulation to another, careful monitoring of clinical response and attention to the need for dose adjustment are warranted.

A major milestone in the treatment of epilepsy occurred in the late 1960s when the measurement of serum levels of antiepileptic drugs (AEDs) was introduced as a tool to tailor dosage to individual needs. Therapeutic drug monitoring has been invaluable in identifying causes for variability in AED levels, which include genetic profile, age, pregnancy, concomitant disease, and drug–drug interactions (Patsalos et al, 2008).
Routine monitoring of drug levels also led to the realization that the drug concentration in serum fluctuates considerably during a dosing interval for those AEDs that are absorbed and eliminated rapidly. Since the concentration in serum usually correlates with the concentration at the site of action, these fluctuations may result in transient side effects at the time of peak concentration and a potential fall to subtherapeutic levels at the trough (Pellock et al, 2004 and Bialer, 2007).

An effective strategy to minimize fluctuations in serum drug levels is to reduce the interval between doses. However, taking medications three or four times daily is inconvenient and may adversely affect compliance (Claxton et al., 2001). These drawbacks provide the rationale for developing extended-release formulations, which are intended to ensure relatively stable serum concentrations with less frequent administrations, typically once or twice daily (Bialer, 2007).

Extended-release formulations are available for several AEDs, and their number is increasing steadily.

**Serum Level Profile as an indicator of a Drug’s Concentration at the Site of Action:**

The scientific prerequisites for developing extended-release formulations of AEDs are that fluctuations in serum drug levels should reflect comparable fluctuations at the site of action and that minimizing such fluctuations is expected to be clinically beneficial.

In fact, only a few studies have investigated the relationship between drug concentrations in serum and in the brain over time. This relationship can be complex, partly because transfer across the blood–brain barrier is not equally rapid among AEDs. Because of the presence of binding proteins and transporter systems, there also can be important differences in drug concentrations among the blood, the CSF, and the brain as well as within discrete brain areas (Patel et al., 2009).

Overall, available data suggest that changes in serum AED concentrations are not necessarily mirrored by parallel changes in CSF or brain concentrations and that fluctuations in drug levels in the brain may be less prominent than in blood.

**Serum Concentration profile of an AED and its Clinical Response (Effect):**

For a simple and direct relationship to exist between the serum concentration profile of an AED and its effect, at least two conditions must be met:

1) The concentration profile at the site of action should mirror that in serum and
2) The drug action must be rapid and reversible, with an intensity of effect proportional to the drug’s concentration at the site of action.

The first of these conditions does not necessarily apply to all AEDs, because passage across the blood–brain barrier may be relatively slow and drug distribution between the blood and discrete brain compartments may be quite complex. The relationship between serum drug concentration and effect, in turn, is dependent on the drug’s mechanism of action.

Investigations into the relationship between the serum drug level profile and the time course of antiepileptic effect in humans are scarce because of difficulties in assessing seizure protection at precise time points. However, available evidence suggests that this relationship also can be complex.

In an elegant study that used suppression of the photoparoxysmal response as a measure of anticonvulsant effect after single doses of valproate in patients with epilepsy, Rowan and coworkers demonstrated that the effect, on average, appeared 3 h (range, 1–5 h) after the peak serum drug concentration and lasted for up to 5 days, when the drug was no longer detectable in blood (Rowan et al, 1979).

While these results may not apply to other clinical settings (e.g., the treatment of status epilepticus), the reported effectiveness in some patients of once daily dosing with immediate-release valproate indicates that the duration of effect can exceed the half-life of the drug (Covanis and Jeavons, 1980).

The photoparoxysmal model also has been applied to assess the time course of action of newer AEDs, including levetiracetam (Kasteleijn-NolstTrenité et al, 1996), brivaracetam (Kasteleijn-NolstTrenité et al, 2007), and carisbamate (Kasteleijn-NolstTrenité et al, 2007). With these agents, the onset of effect was consistent with the appearance of the drug in serum, but at the highest doses, the response lasted for much longer than the drug’s half-life. This observation provided the rationale for selecting a twice-daily dosing scheme in the clinical development of Levetiracetam.

It should be noted that a duration of action that is longer than a drug’s half-life does not necessarily imply the existence of an indirect or irreversible mechanism of action. When a drug is
well tolerated at serum levels far in excess of the minimally effective concentration, intake of large doses at intervals longer than the drug’s half-life will ensure sustained therapeutic cover without adverse effects.

In fact, multiple daily doses, or extended-release formulations, are most useful in the case of drugs for which high peak serum concentrations are associated with significant adverse effects.

2.5 Once Daily Dosing with Anti-Epileptic Drugs: Advantages and Concerns

Some extended-release products can be taken once daily. In addition to convenience, this regimen may be associated with subtle psychological benefits, particularly for those patients who are seizure-free and perceive each pill-taking act as an unpleasant reminder of their disease. Less frequent dosing also can improve compliance.

A systematic review of results from 76 studies found that mean dose-taking compliance increased from 51% with four to 65% with three to 69% with two times a day dosing and to 79% with once-daily dosing, although the differences between once and twice daily or between twice and three times a day dosing were not statistically significant (Claxton et al, 2001).

While compliance is best with one daily dose, the risks of seizure recurrence after missing a dose may also be greatest. The ability of a product to allow omission of a dose without adverse consequences, the so-called “forgiveness period,” can be defined as the post-dose duration of action minus the dosing interval (Bialer, 2007). Extended-release products may not sustain effective serum drug levels for much longer than 24 h, and therefore, missing a dose could result in insufficient therapeutic cover for many hours.

2.6 Levetiracetam in the treatment of epilepsy

Epilepsy is a common chronic disorder that requires long-term antiepileptic drug therapy. Approximately one half of patients fail the initial antiepileptic drug and about 35% are refractory to medical therapy, highlighting the continued need for more effective and better tolerated drugs (Bassel Abou-Khalil, 2008).

Levetiracetam is an antiepileptic drug marketed since 2000. Its novel mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein
SV2A in the brain. Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver. The availability of an intravenous preparation is yet another advantage (Bassel Abou-Khalil, 2008).

Levetiracetam has been demonstrated to be effective as adjunctive therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy. In addition, it was found equivalent to controlled release carbamazepine as first-line therapy for partial-onset seizures, both in efficacy and tolerability. Its main adverse effects in randomized adjunctive trials in adults have been somnolence, asthenia, infection, and dizziness. In children, the behavioral adverse effects of hostility and nervousness were also noted. Levetiracetam is an important addition to the treatment of epilepsy (Bassel Abou-Khalil, 2008).

2.7 Levetiracetam pharmacology

Levetiracetam is rapidly and almost completely absorbed after oral intake, with peak plasma concentrations approximately one hour after oral administration. Food reduces the peak plasma concentration by 20% and delays it by 1.5 hours, but does not reduce Levetiracetam bioavailability (Patsalos, 2000 and 2003). There is a linear relationship between Levetiracetam dose and Levetiracetam serum level over a dose range of 500–5000 mg (Radtke, 2001). Levetiracetam protein binding, at less than 10%, is not clinically relevant. Levetiracetam metabolism is not dependent on the liver cytochrome P450 enzyme system. Levetiracetam is predominantly excreted unchanged through the kidneys, with only about 27% metabolized. The main metabolic pathway is hydrolysis of the acetamide group in the blood (Radtke, 2001). The resultant metabolite generated is inactive. Levetiracetam plasma half-life is 7 ± 1 hours in adults, but can be prolonged by an average of 2.5 hours in the elderly, most likely due to decreased creatinine clearance with age (French, 2001 and Hirsch et al, 2007). In patients with impaired renal function, a dose adjustment is needed, dependent on the creatinine clearance (French, 2001).

The absence of hepatic metabolism and of protein binding predict absence of pharmacokinetic interactions (Nicolas et al, 1999). Indeed, no pharmacokinetic interactions were observed with phenytoin, warfarin, digoxin, or oral contraceptives (Browne et al, 2000; Levy et al, 2001; Patsalos, 2000 and 2003; Ragueneau-Majlessi et al, 2001 and 2002; Abou-Khalil et al, 2003 and Coupez et al, 2003).
However, some studies have suggested lower Levetiracetam levels or higher Levetiracetam clearance in patients taking enzyme-inducing AEDs (May et al, 2003; Perucca et al, 2003 and Hirsch et al, 2007). Autoinduction probably does not occur with Levetiracetam, but one study involving short intensive monitoring suggested a drop in serum levels after the fifth day of administration (Stefan et al, 2006).

2.8 Serum levels of Levetiracetam

Levetiracetam has linear kinetics, such that in any individual the serum concentration is proportional to the dose (Patsalos, 2004). However, the effective serum level for Levetiracetam is not known.

One study in 69 patients taking 500–3000 mg/day found that the trough plasma concentration ranged from 1.1 to 33.5 μg/mL (Lancelin et al, 2007). Similar mean concentrations were found in patients experiencing adverse effects and those without adverse effects (11.2 vs 10.9 μg/mL). The mean plasma concentrations in responders and non-responders were 12.9 and 9.5 μg/mL. The difference was not significant, but the authors suggested that 11 μg/mL could be a threshold concentration for a therapeutic response. The vast majority of patients in this study had refractory epilepsy, making it difficult to study the effective plasma concentration of Levetiracetam. Such a study is best conducted in patients with new onset epilepsy.

A trial comparing Levetiracetam and carbamazepine in newly diagnosed patients did not report plasma concentrations (Brodie et al, 2007). However, it found that most patients were seizure-free at the lowest Levetiracetam dose of 1000 mg/day. In the therapeutic drug monitoring study mentioned earlier, a daily dose of 1000 mg/day was associated with a mean trough level of 6.5 ± 2.4 μg/mL (Lancelin et al, 2007).

Even though a therapeutic and toxic Levetiracetam concentration are not defined, measuring the serum concentration is helpful to assess compliance. In addition, if a baseline serum concentration is obtained during a period of good seizure control, the serum concentration can be repeated with breakthrough seizures to assess if a drop in concentration played a role. Finally, monitoring serum concentration through the course of pregnancy can help with calculating the recommended dose adjustments needed to correct for increased clearance.
2.9 Putative mechanism of action of Levetiracetam

Levetiracetam is different in its mechanism from that of other AEDs, because it is not effective in the standard animal models used to screen for anticonvulsant activity, while it is effective in the chronic kindling model (Loscher and Honack, 1993 and Klitgaard et al, 1998).

It was recently established that the most relevant Levetiracetam mechanism of action is through binding to the synaptic vesicle protein SV2A (Lynch et al, 2004). The SV2A binding affinity of Levetiracetam derivatives correlated strongly with their binding affinity in the brain, as well as with their ability to protect against seizures in the audiogenic mouse model (Lynch et al, 2004).

Similar findings were noted in the mouse corneal kindling model and the GAERS rat model of generalized absence epilepsy (Kaminski et al, 2008). The specific effect of Levetiracetam binding to SV2A appears to be a reduction in the rate of vesicle release (Yang et al, 2007).

Levetiracetam has other mechanisms of action that likely play a comparatively smaller role: reversing the inhibition of neuronal GABA- and glycine-gated currents by the negative allosteric modulators zinc and β-carbolines (Rigo et al, 2002), and partial depression of the N calcium current (Niespodziany et al, 2001 and Lukyanetz et al, 2002). At present, the mechanisms of action have not yet helped identify a specific clinical efficacy profile for Levetiracetam.

2.10 Levetiracetam efficacy as adjunctive therapy in refractory partial epilepsy in adults – pivotal double-blinded randomized controlled trials

Levetiracetam was found efficacious in 3 pivotal placebo-controlled randomized blinded clinical trials in adults with refractory partial epilepsy. These trials investigated three doses, 1000, 2000, and 3000 mg/day. All three doses were found to be effective.

The US trial compared 1000 mg/day and 3000 mg/day (in two divided doses) with placebo (Cereghino et al, 2000). The study randomized 294 patients, 268 of whom completed the 14 weeks of treatment. After a 12-week single-blind baseline, Levetiracetam was titrated over 4 weeks. Patients in the 1000 mg/day group first received 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks, while patients in the 3000 mg/day group received 1000 mg/day for 2 weeks and then 2000 mg/day for 2 weeks. The median percentage reduction in seizures over baseline was 32.5% for Levetiracetam 1000 mg/day and 37.1% for Levetiracetam 3000 mg/day as compared with 6.8% for placebo. The 50% responder rates were 33% for 1000 mg/day and 39.8% for 3000 mg/day, compared with 10.8% for placebo. Seizure freedom was noted in 3% of patients
in the 1000 mg group and 8% of the 3000 mg group. No patients were seizure-free in the placebo group. Maximum efficacy was already present in the first visit 2 weeks after initiating titration.

The European placebo-controlled randomized double-blind trial compared 2000 mg/day, 1000 mg/day, and placebo as add-on treatment (Shorvon et al, 2000). Patients randomized to 2000 mg/day received 500 mg bid for 2 weeks, then 1000 mg bid while patients randomized to 1000 mg/day received placebo for 2 weeks, then 500 mg bid. The 4-week titration period was followed by a 12-week maintenance phase. Out of 324 randomized patients, 278 completed the study. There was a 26.5% median seizure reduction from baseline for the 2000 mg/day group, 17.7% for the 1000 mg/day group, and 6.1% for the placebo group. The 50% responder rate was 31.6% for the 2000 mg/day group, 22.8% for the 1000 mg/day group, and 10.4% for the placebo group. Two percent of the 2000 mg patients, 5% of the 1000 mg patients, and 1% of the 112 mg placebo patients were seizure free. In both the US and European trials, both doses tested were more efficacious than the placebo, but were not significantly different from each other.

A third pivotal trial, also conducted in Europe, only compared 3000 mg per day to a placebo (Ben-Menachem et al, 2000). After the baseline phase, patients randomized to Levetiracetam received 1000 mg/day for 2 weeks, then 2000 mg/day for 2 weeks before receiving 3000 mg/day for the remainder of the trial. The median reduction in seizure frequency from baseline was 39.9% for Levetiracetam compared with 7.2% for placebo. The responder rate was 50% for Levetiracetam compared with 16.7% for placebo. Seizure freedom was reported in 8.2% of Levetiracetam patients compared with 1% of placebo patients.

The findings from the above trials were confirmed in a smaller blinded trial (94 patients) conducted in Taiwan, comparing adjunctive 2000 mg/day of Levetiracetam to placebo (Tsai et al, 2006). The responder rate in the Levetiracetam group was 53.5% compared with 10.6% in the placebo group. Seizure freedom was observed in 8.7% of Levetiracetam patients, but none of the placebo patients.

The three main pivotal trials received a number of post hoc analyses. Two of these analyses addressed the latency for onset of action of Levetiracetam. In one study, it was found that the increase in proportion of seizure-free patients over baseline was 15% for the first day of treatment and 17% for second and third days of treatment for 1000 mg/day, all statistically significant (French and Arrigo, 2005). However the increases for 333 mg/day were 7% for Day 1 and 9% for the second and third days. These were not significant. There were no major changes in the placebo group. In a second analysis, the mean proportion of seizure-free days were as computed
during each week after initiation of treatment (French et al, 2005). The mean proportion of seizure-free days was greater in the Levetiracetam than the placebo group and the difference was observed as early as the first week after initiation of treatment. Interestingly, it was also greatest at that point in time, after which it dropped but remained fairly stable. A similar observation was made in the Taiwanese study, with initial 69% reduction in seizure frequency at the 2-week visit after starting Levetiracetam, compared with only 37.5% reduction at the end of the study (Tsai et al, 2006).

Another post hoc analysis addressed the number of seizure-free days (Leppik et al, 2003). Addition of Levetiracetam increased the number of days without seizures by 5.19 per quarter. An additional analysis addressed the affect of Levetiracetam on subtypes of partial seizures in the pooled data from the three major pivotal trials (Leppik et al, 2003). A statistically significant reduction in the frequency of all partial seizures subtypes was observed. In addition, there was an independent reduction of secondarily generalized seizures over and above the reduction of partial seizures.

2.11 Long-term maintenance of efficacy with Levetiracetam

The report of development of tolerance in one animal model of epilepsy (Loscher and Honack, 2000) prompted evaluation of Levetiracetam long-term efficacy in patients with epilepsy.

Some of the long-term studies analyzed the trial data and others analyzed post marketing data. In the analysis of the trial data base, the continuation rate was 60% after 1 year (Krakow et al, 2001). Factors that predicted continuation of Levetiracetam were a high maximal dose, a low starting dose, the presence of generalized tonic-clonic seizures, and a smaller number of AEDs at baseline. Thirteen per cent of the patients became seizure free for at least 6 months and 8% for at least 1 year; 4.5% of patients became seizure free from the first day of exposure until the cut-off point. The total trial population was divided into cohorts based on the duration of exposure (6-month increments) and the median percentage reduction in seizure frequency was examined for each of the cohorts (Ben-Menachem et al, 2003). Overall, the median percentage reduction was 39.6% and there was no decline in that parameter within each cohort. In fact, the median percent reduction appeared to increase rather than decrease over time. During the last 6 months of treatment 11.7% of patients were seizure free overall. The stability of response was also evaluated by examining the percentage of responders in the first 3 months who remained responders in the subsequent 3 months and the percentage of the latter who remained responders for the next 3 months (Abou-Khalil and Lazenby, 2003). The analysis indicated that 73.6% of the 3-month responders remained responders for the next three months and 82% of these were still
responders in the subsequent 3 months. Thus, Levetiracetam response appears to be maintained for the majority of patients, but a small percentage of individuals may have a reduction in benefit while others may have an improvement.

The post-marketing studies had a similar conclusion (Abou-Khalil and Lazenby, 2003; Betts et al, 2003; Ben-Menachem and Gilland, 2003; Nicolson et al, 2004; Depondt et al, 2006 and Kuba et al, 2006). The retention rates at 1 year varied from 61% to 77% and seizure freedom rate varied from 16% to 26%. In one study, there was a slight reduction in seizure freedom from 32% at 6 months to 26% at 1 year ( Betts et al, 2003); among patients who were seizure free at 6 months, 74% were still seizure free at 1 year and 18% were still more than 90% improved, though no longer seizure free. Another study with follow-up for 1 to 2 years, 81.5% of patients who were seizure free in the first 3 months were still seizure free in the last 3 months of treatment, but 39% of those who were seizure free in the last 3 months were not seizure free in the first 3 months (Abou-Khalil and Lazenby, 2003).

The phenomenon of AED tolerance may possibly be playing a role in a small proportion of patients treated with Levetiracetam. This phenomenon is recognized with other antiepileptic drugs as well, but its degree is not clearly understood (Loscher and Schmidt, 2006).

### 2.12 Levetiracetam tolerability

The initial placebo-controlled adjunctive trials in partial epilepsy suggested that treatment emergent adverse events that had a higher frequency with Levetiracetam were somnolence, asthenia, dizziness, and infection (upper respiratory infections).

Somnolence was the most common reason for Levetiracetam discontinuation in the US pivotal partial seizure trial (Cereghino et al, 2000). Its frequency ranged from 5% to 20% in the adult pivotal trials (Ben-Menachem and Falter, 2000; Cereghino et al, 2000; Shorvon et al, 2000; Berkovic et al, 2007; Brodie et al, 2007 and Noachtar et al, 2008), and 23% in the pediatric trial (Glauser et al, 2006).

The most common adverse events did not seem dose related in the studies that evaluated more than one Levetiracetam dose (Cereghino et al, 2000 and Shorvon et al, 2000). However, in one study comparing 2,000 and 4,000 mg/day without titration, somnolence was highest in patients receiving 4,000 mg/day, affecting 44.7% (Betts et al, 2000).
Adverse effects generally appeared within the first month of treatment. In one trial somnolence was reported in 10% of patients during Levetiracetam up-titration, but not in the evaluation period (Noachtar et al, 2008). Drowsiness seems more common in older age. In one post-marketing study comparing 151 younger adults (age 16–31 years) and 157 older adults (age 55–88 years), drowsiness was reported by 12% of the younger and 24.7% of the older group. It resulted in dose reduction or discontinuation in 6.9 and 3.1% of the younger group and 15.1% and 5.2% of the older group.

Behavioral/psychiatric adverse effects were not prominent in the initial adjunctive therapy trials in partial epilepsy. However, these were more prominent in subsequent trials performed in less refractory patients (Abou-Khalil et al, 2003). In a systematic review of Levetiracetam safety in the clinical trial population, non-psychotic behavioral symptoms occurred in 13.5% of Levetiracetam-treated patients with epilepsy versus 6% of placebo-treated patients (French et al, 2001). The difference between placebo and Levetiracetam groups was small or non-existent in cognitive and anxiety studies, suggesting that behavioral adverse effects may be specific for epilepsy. It is also possible that the greater occurrence in epilepsy patients could be contributed to by higher dose in the epilepsy group. The non-psychotic behavioral symptoms that occurred in more than 1% of epilepsy patients in placebo-controlled trials were depression (3.8%), nervousness (3.8%), hostility (2.3%), anxiety (1.8%), and emotional lability (1.7%) (Cramer et al, 2003). The proportion of patients with these symptoms was somewhat higher in an open-label study that included less refractory patients (Abou-Khalil et al, 2003). Among 219 patients in that study nervousness was reported in 9.6%, depression in 7.3%, hostility in 4.1%, personality disorder in 3.7%, emotional lability in 2.7%, and anxiety in 2.3% of subjects (Abou-Khalil et al, 2003). Behavioral adverse events were severe in 7 of 219 patients (3.2%).

Behavioral adverse events may be more likely in certain patient groups. Learning disabilities were a predisposing factor in one study that reported a 23% frequency of behavioral adverse effects when learning disability was present compared to 10% if learning disability was absent (Brodtkorb et al, 2004). One other study indicated a greater frequency of behavioral adverse effects in patients with previous psychiatric history, history of febrile convulsions, and a history of status epilepticus, and a lower frequency when lamotrigine was used concomitantly with Levetiracetam (Mula et al, 2003, 2004). Similar risk factors were noted for psychiatric adverse effects with topiramate, suggesting that a subgroup of patients is generally prone to develop these adverse effects during AED therapy, independent of AED mechanism of action (Mula et al, 2007).
Behavioral adverse events are most often mild and are not usually a cause of Levetiracetam discontinuation. However, behavioral adverse effects had a greater representation in patients who discontinued Levetiracetam, and may be the most common reason for discontinuation (Abou-Khalil and Lazenby, 2003). In one large case controlled study, more than half of the patients who discontinued Levetiracetam did so because of behavioral issues, the most important of which were depression, irritability, and aggression (White et al, 2003). Patients who discontinued Levetiracetam because of behavioral adverse events were more likely to have symptomatic generalized epilepsy, history of psychiatric diagnosis, and a faster Levetiracetam titration (White et al, 2003). Behavioral adverse experiences were reported with a higher frequency in pediatric studies. In the pivotal pediatric adjunctive placebo-controlled trial, 5 behavioral/psychiatric adverse effects were reported in >5% of patients: hostility (12% of Levetiracetam and 6% of placebo), nervousness (10% of Levetiracetam vs 2% of placebo), personality disorder (8% of Levetiracetam vs 7% of placebo), emotional lability (6% of Levetiracetam vs 4% of placebo), and agitation (6% of Levetiracetam, 1% of placebo). None of these adverse events were seen in >5% of patients in the adult adjunctive partial epilepsy trials. In the adjunctive generalized epilepsy trial, irritability occurred in 6.3% and mood swings in 5.1% of Levetiracetam-treated patients versus 2.4% and 1.2% of placebo-treated patients (Berkovic et al, 2007). However, in the myoclonic seizure trial nervousness was reported in 3.3% of Levetiracetam-treated and 6.7% of placebo patients. In the newly diagnosed epilepsy trial, the main behavioral adverse effect reported was depression in 6.3% of Levetiracetam patients and 2.1% of carbamazepine-treated patients (Brodie et al, 2007).

Behavioral adverse effects were reported more often in pediatric than adult case series (Glauser et al, 2002; Wheless and Ng, 2002 and De Los Reyes et al, 2004). However, improvements in behavior were also common. In one study, 12.8% of children demonstrated aggression and 10.3% hyperactivity, but 25.6% had an improvement in behavior and/or cognition (Wheless and Ng, 2002).

Psychosis has been reported rarely with Levetiracetam therapy (Kossoff et al, 2001; Motamedi et al, 2003 and Youroukos et al, 2003). The symptoms were always reversed with Levetiracetam discontinuation. Psychosis may occur rarely with many AEDs, and is unlikely to be specific for Levetiracetam.

It is of note that Levetiracetam is not associated with serious systemic adverse effects. One common concern, allergic rash is uncommon with Levetiracetam. In one large post-marketing
study, the risk of rash with Levetiracetam use was 0.6%, significantly lower than the average of all AEDs (Arif et al, 2007).

Safety in pregnancy and breast feeding-

Limited data are available on safety in pregnancy. In the analysis of the UK Epilepsy and Pregnancy Registry, 3 of 117 exposed pregnancies had a major congenital malformation, but all three were also exposed to other AEDs (Hunt et al, 2006). There were also no minor malformations in the Levetiracetam monotherapy group which included 39 monotherapy exposures. Other smaller reports also did not identify any Levetiracetam-related malformations (Long, 2003 and Ten Berg et al, 2005). Four infants exposed to Levetiracetam monotherapy had a low birth rate, but the mean birth weight for infants exposed to Levetiracetam was within the normal range (Hunt et al, 2006). Thus, preliminary data seemed favorable, but additional reports are needed for definitive assessment of Levetiracetam safety during pregnancy.

Levetiracetam is extensively transferred from mother into breast milk. However, breast fed infants had very low Levetiracetam serum concentrations, suggesting that breastfeeding should not be contraindicated (Johannessen et al, 2005 and Tomson et al, 2007).

Quality of life-

Quality of life measurements were incorporated in the US pivotal Levetiracetam trial. The QOLIE-31 questionnaire was administered at the end of the baseline period before randomization and again at the end of the treatment period. It showed improvement in 3 of the 7 items: overall quality of life, seizure worry, and cognitive functioning (Cereghino et al, 2000). The results were analyzed in greater detail in a separate publication (Cramer et al, 2000). Statistically significant improvements were found in seizure worry and overall quality of life in the Levetiracetam treatment group. The placebo group scores decreased for the cognitive functioning subscale and the total score. QOLIE scores were influenced by seizure control. Patients who had a 50% or greater improvement in seizures had significant improvements in all areas compared with non-responders. The exception was medication effect. Therefore, Levetiracetam seemed to have a positive impact on health-related quality of life.

One hundred and one patients who completed QOLIE-31 at the end of double-blind treatment also completed the questionnaire during a long-term follow-up visit, approximately 4 years after starting Levetiracetam (Cramer and Van Hammee, 2003). All scales and the total score improved between the baseline and long-term assessments. The short-term improvement noted at the end
of the double-blind treatment period was maintained in the long term, and patients who were randomized to placebo reached the same level of improvement in the long-term as patients who initially received Levetiracetam.

One recent study used QOLIE-31 at baseline, at 16 weeks of double-blind add-on treatment, then again at 40 weeks of treatment (now open treatment). Fourteen patients were randomized to Levetiracetam and 14 to placebo. Subscale scores on the QOLIE-31, including scores on Cognitive Functioning and Social Function improved only for the Levetiracetam group at the end of short-term treatment. At the end of the long-term phase, these improvements were maintained (Zhou et al, 2008).

Cognitive function-

Levetiracetam cognitive effects were examined in comparison to carbamazepine (CBZ) in 28 healthy volunteers, using a randomized, double-blind, two-period crossover design (Meador et al, 2007). The doses were adjusted to mid-range therapeutic level, with a mean of 7.5 μg/mL for CBZ and 32.2 μg/mL for Levetiracetam. CBZ was worse than Levetiracetam on 15 of 34 variables tested, and better at none. Compared with baseline, CBZ was worse for 26 of 34 variables, and Levetiracetam was worse for 4 (Meador et al, 2007).

There is no evidence of decline in cognitive function with Levetiracetam treatment in patients with partial epilepsy. One study compared Levetiracetam with topiramate (TPM) using standardized a neuropsychological test battery. Testing was performed before treatment and after reaching steady state in 30 consecutive patients with focal epilepsy treated with LEV and 21 treated with TPM. Whereas the TPM group worsened in cognitive speed, verbal fluency, and short-term memory, there was no change in the Levetiracetam group (Gomer et al, 2007).

Another study found that performance time on the Wisconsin Card Sorting Test and Delayed Logic Memory significantly improved for 14 patients randomized to Levetiracetam, but not for 14 randomized to placebo (Zhou et al, 2008).

2.13 Place of Levetiracetam in epilepsy therapy

Partial epilepsy:

Levetiracetam has not been compared directly to other new AEDs, but meta-analysis of controlled partial epilepsy adjunctive trials suggested that Levetiracetam had a favorable ‘responder-withdrawal ratio’ in comparison with other agents (Marson et al, 2001; Otoul et al, 2005 and
Zaccara et al, 2006). Based on the favorable efficacy and tolerability of Levetiracetam as an add-on therapy in refractory partial epilepsy, it is reasonable to consider it one of the first add-on therapies in these patients. Other factors that argue for this are the absence of drug–drug interactions and the rapid onset of action, which means that it will rapidly become clear whether Levetiracetam will be effective. However the choice of therapy is influenced by many factors including co-morbidity. The co-morbidity of obesity, for example, may favor adjunctive therapy with an AED that can cause weight loss, for example topiramate or zonisamide. Psychiatric co-morbidity may also argue against choosing Levetiracetam as initial adjunctive therapy.

The place of Levetiracetam as an initial monotherapy is less clear cut. There is now a well designed monotherapy study that showed non-inferiority to controlled-release carbamazepine (Brodie et al, 2007), likely to satisfy the criteria of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society for initial monotherapy use (French et al, 2004). Levetiracetam has approval by the European Medicines Agency but not the US FDA for initial monotherapy for partial onset seizures. Despite the absence of US FDA approval, there is ample evidence that Levetiracetam is widely used in the hospital setting for new onset epilepsy and acute seizures (Chabolla et al, 2003; Glass et al, 2005; Falip et al, 2006; Di Bonaventura et al, 2006 and Szaflarski et al, 2007). This was the case even before the appearance of the intravenous formulation, but the intravenous formulation certainly has made this use more prevalent. The other antiepileptic drugs with intravenous formulations have associated disadvantages. Phenobarbital is highly sedating and both phenobarbital and phenytoin/fosphenytoin are enzyme inducing and could result in important unfavorable interactions. Intravenous valproate is safe and well tolerated, but potential adverse effects with long-term valproate use may be a deterrent to its use in hospitalized patients. As a result of the above, Levetiracetam has become frequently used in patients with seizures secondary to stroke, neurosurgical intervention, brain tumors, and other medical conditions (Chabolla et al, 2003; Wagner et al, 2003; Glass et al, 2005; Di Bonaventura et al, 2006; Falip et al, 2006; Newton et al, 2006, 2007; Maschio et al, 2006 and Szaflarski et al, 2007).

The IV formulation of Levetiracetam is currently approved for temporary replacement in patients who cannot take oral medication (Ramael et al, 2006 and Baulac et al, 2007). It is not approved for the treatment of status epilepticus. However, there are now several reports of the use of Levetiracetam (usually oral Levetiracetam) in refractory status epilepticus (Atefy and Tettenborn, 2005; Rossetti and Bromfield, 2005; Patel et al, 2006; Rossetti and Bromfield, 2006; Rupprecht et al, 2007 and Schulze-Bonhage et al, 2007), and it is certainly reasonable to consider IV
Levetiracetam as one of the options for patients with non-convulsive partial status epilepticus as well as refractory status epilepticus, particularly in those patients who have recurrence of status in conjunction with anesthesia withdrawal. Levetiracetam may also play a role for patients who have to be started or restarted on Levetiracetam abruptly. The intravenous administration of Levetiracetam is associated with a peak level at the end of infusion in 5 or 15 minutes, whereas the oral administration is associated with a peak at 1 hour, and the peak would be delayed if administration is with food (Ramael et al, 2006).

**Generalized epilepsy:**

There is now definite evidence of Levetiracetam efficacy as adjunctive therapy for patients with idiopathic generalized epilepsy and uncontrolled generalized tonic-clonic seizures or generalized myoclonic seizures (Berkovic et al, 2007 and Noachtar et al, 2008). Levetiracetam can therefore be considered as an early adjunctive therapy in these conditions. In the case of myoclonic seizures, it is the only new antiepileptic drug with an FDA approved indication for this application (one older antiepileptic drug, clonazepam, also has FDA approval for myoclonic seizures).

Levetiracetam has no FDA indication and no pivotal trials supporting initial monotherapy use in generalized epilepsy. However, the evidence of adjunctive efficacy in juvenile myoclonic epilepsy has prompted use as initial monotherapy in juvenile myoclonic epilepsy. The anecdotal data has been very favorable (Specchio et al, 2006 and Sharpe et al, 2008). However, the use of Levetiracetam as initial monotherapy cannot be strongly supported without a pivotal trial, for example a trial comparing it with valproate. In women of childbearing potential, valproate use is associated with unacceptable risks including teratogenicity in the event of pregnancy, weight gain, hair loss, and hormonal changes. As a result of these risks, it has become common in practice to use alternatives such as lamotrigine, topiramate, and zonisamide (Prasad et al, 2003). None of these drugs have pivotal trials supporting their use for juvenile myoclonic epilepsy. Levetiracetam could be added to that list, with the advantage of definitive evidence for efficacy as add-on therapy. The one seizure type for which there is no data is absence seizures. Based on lack of data, Levetiracetam would not be an appropriate initial therapy for absence seizures or an early adjunctive agent for refractory absence seizures.

**Status epilepticus:**

Intravenous Levetiracetam may be considered in the treatment of nonconvulsive or focal status epilepticus refractory to initial therapy. In this setting, the risk of general anesthesia may outweigh the risk of neuronal injury from ongoing seizure activity, such that additional nonsedating
antiepileptic therapy may be used. The dose of intravenous Levetiracetam should probably be 1000–1500 mg administered over 5 minutes. Generalized convulsive status epilepticus should be treated with standard intravenous therapy (usually lorazepam followed by fosphenytoin or phenytoin). General anesthesia should be considered next if initial therapy is not effective. Levetiracetam may be used only if it can be added without delaying standard therapy or general anesthesia when standard therapy fails.

2.14 Levetiracetam Dosing recommendations

The prescribing information recommends an adult starting dose of 1000 mg/day (500 mg twice daily), with subsequent escalation by 1000 mg every 2 weeks up to 1500 mg twice daily. These recommendations are based on the dose used in pivotal trials.

In patients at higher risk for behavioral – psychiatric adverse effects, the starting dose can even be smaller, at 250 mg at bedtime. The same approach can be used with the elderly who have a higher chance of experiencing adverse effects on Levetiracetam. A starting dose of 500 mg twice daily can still be considered in hospitalized patients who need faster efficacy. Automatic escalation of the Levetiracetam dose to 3000 mg/day is usually not necessary. In patients with infrequent seizures, for whom the minimal effective dose can be hard to determine, the Levetiracetam dose can be escalated to 1000 mg twice daily. The dose of Levetiracetam can be increased up to 3000 mg/day for persistent seizures. Even though there is no clear benefit beyond 3000 mg/day, the Levetiracetam dose can be increased to 4000 mg/day for patients who have clearly responded to Levetiracetam, but have residual breakthrough seizures. However, the treating physician has to be aware of the risk of seizure exacerbation at higher Levetiracetam doses.

The same dosing guidelines can be applied to children. The official prescribing information recommends starting at 20 mg/kg/day in 2 divided doses, with subsequent increments of 20 mg/kg every 2 weeks up to 60 mg/kg/day. However, starting at 10 mg/kg may reduce the frequency or intensity of behavioral adverse effects and provide a greater opportunity to manage these adverse effects rather than stop Levetiracetam. The target dose should be tailored to the patient, such that escalation to 60 mg/kg/day may not be necessary.

In summary, Levetiracetam should be considered as an initial or early add-on therapy for partial epilepsy, initial or early add-on therapy for myoclonic seizures in patients with juvenile myoclonic epilepsy, and as an early add-on therapy for patients with generalized tonic-clonic seizures in the setting of idiopathic generalized epilepsy. There is also evidence to support use of Levetiracetam as initial monotherapy in partial epilepsy, but other indications are not supported by pivotal trials.
2.15 Clinical Pharmacology (Levetiracetam IR)

2.15.1 Pharmacodynamics -

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of \(\alpha\)-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. It has recently been reported that levetiracetam reduces high voltage activated \(\text{Ca}^{2+}\) currents, reverses inhibition of GABA and glycine gated currents induced by negative allosteric modulators (zinc and \(\beta\)-carbolines), and effects voltage gated potassium channel conductance, suggesting that its mechanism of action differs from other antiepileptic drugs (Shorvon and Rijckevorsel, 2002).

Furthermore, levetiracetam has been shown in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis (LaRoche and Helmers, 2004). The interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the levetiracetam.

2.15.2 Pharmacokinetics (PK) -

**Absorption**

Following oral administration in fasted subjects, absorption of Levetiracetam is rapid and complete, with peak plasma concentrations occurring in about an hour [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].

Food does not affect the extent of absorption of Levetiracetam but it decreases \(C_{\text{max}}\) by 20% and delays \(T_{\text{max}}\) by 1.5 hours and may be taken with or without food. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].

Steady state is achieved after 48 hours of multiple twice-daily dosing [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012; and Cramer et al, 2002]. There was no evidence of unexpected accumulation of as evidenced by the mean ratio of 1.6 of AUC\(_{0-12h}\) at steady state to AUC\(_{0-12h}\) after single dose; the theoretical value (R) is 1.4. Elimination half-life does not vary with dose, the route of administration, or after multiple dosing. There were no noteworthy changes in
pharmacokinetics, including urinary excretion, after repeated dosing [ABPI Compendium Sheet, KEPPRA (Levetiracetam). UCB Pharma Limited. UK, August 2006].

**Distribution**

Levetiracetam and its major metabolite are less than 10% bound to plasma proteins. The volume of distribution of Levetiracetam is approximately 0.5 to 0.7 l/kg (Patsalos, 2004), a value close to the total body water volume.

**Metabolism**

Levetiracetam is not extensively metabolized in humans. Unlike some other AEDs, Levetiracetam is not metabolized in the liver; instead, it is transformed by enzymatic hydrolysis of the acetamide group in the blood to inactive carboxylic acid metabolite, ucb L057 (24% of dose) and two minor metabolites, none of them is active [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].

**Elimination**

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. The mean total body clearance is 0.96 ml/min/kg. The major route of excretion is via urine, Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012]. The renal clearance of Levetiracetam and its metabolite, ucb L057 is 0.6 and 4 ml/min/kg respectively [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012] indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance. The plasma concentration of Levetiracetam is generally higher in the elderly and in patients with renal impairment.

**PK in the Elderly**

Pharmacokinetics of Levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects (Table 2) [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].
# Chapter 2

## Review of Literature

### Table 2. Levetiracetam noncompartmental pharmacokinetic parameter values in young adults, geriatric subjects, and pediatric patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Adults (22-28 yrs): 1000mg, single dose</th>
<th>Geriatric subjects (61-88 yr) 500-mg, single dose</th>
<th>Geriatric subjects (61-88 yr) 500-mg, twice daily for 10 days</th>
<th>Pediatric patients (6-12 yr) 20-mg/kg, single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>23.0</td>
<td>19.1</td>
<td>31.2</td>
<td>25.8</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.97</td>
<td>0.97</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>AUC ((µg·h/ml)</td>
<td>222$^a$</td>
<td>251$^a$</td>
<td>248$^b$</td>
<td>241$^a$</td>
</tr>
<tr>
<td>$V_{d/f}$ (L/Kg)</td>
<td>0.7</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>7.8</td>
<td>10.3</td>
<td>10.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Urinary Excretion (% dose) 24 or 48 hrs</td>
<td>51.5</td>
<td>45.5</td>
<td>75$^c$</td>
<td>52</td>
</tr>
<tr>
<td>CL/F (ml/min/kg)$^d$</td>
<td>1.08</td>
<td>0.60</td>
<td>0.60</td>
<td>1.43</td>
</tr>
</tbody>
</table>

$a$ AUC$_{0 \rightarrow \infty}$  

$b$ AUC$_{0 \rightarrow 12h}$  

$c$ Cumulative urinary excretion over 12 hour at steady state.  

$d$ CL/F, Apparent oral clearance

### PK in Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 ml/min [ABPI Compendium Sheet, KEPPRA (Levetiracetam). UCB Pharma Limited. UK, August 2006].
**PK in Renal Impairment**

Because Levetiracetam’s elimination correlates well with creatinine clearance, doses need to be adjusted in patients with renal impairment. Although renal failure markedly prolongs Levetiracetam’s elimination (half-life 25 hrs), it is significantly removed during haemodialysis (50% during a 4-hour session). Dosage should be reduced in patients with impaired renal function receiving Levetiracetam, and supplemental doses should be given to patients after dialysis (Table 3). [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Dosage (mg)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>Mild</td>
<td>50-80</td>
<td>500 to 1,000</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-50</td>
<td>250 to 750</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>250 to 500</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>ESRD patients using dialysis</td>
<td>-</td>
<td>500 to 1,000</td>
<td>Every 24 h*</td>
</tr>
</tbody>
</table>

* Following dialysis, a 250 to 500 mg supplemental dose is recommended.

**PK in Pediatric Population**

In a multicenter, open-label, single-dose study, the pharmacokinetics of the novel antiepileptic drug (AED) Levetiracetam and its major metabolite, ucb L057, were studied in children with partial seizures. In children, the $t_{1/2}$ of Levetiracetam and its metabolite ucb L057 were $6.0 \pm 1.1$ and $8.1 \pm 2.7$ hours, respectively. The $C_{\text{max}}$ and AUC of Levetiracetam equated for a 1-mg/kg dose in children were $1.33 \pm 0.35 \, \mu\text{g/ml}$ and $12.4 \pm 3.5 \, \mu\text{g\cdot h/ml}$ respectively. In adults, $C_{\text{max, norm}}$ was $1.38 \pm 0.05 \, \mu\text{g/ml}$ and $\text{AUC}_{\text{norm}}$ was $11.48 \pm 0.63 \, \mu\text{g\cdot h/ml}$. The apparent body clearance ($1.43 \pm 0.36 \, \text{ml/min/kg}$) was approximately 30-40% higher in children than in adults ($1.43 \, \text{vs.} \, 1.08 \, \text{ml/ min/ kg}$; Table 2). (Pellock et al, 2001).

**Gender Differences**

Gender effects on pharmacokinetics are thought to be likely related to differences in body weight and show no differences when normalized for weight (Table 4). (Stefan et al, 2006)
The most frequently reported adverse reactions are dizziness, somnolence, headache and postural dizziness. In the pooled analysis, there was no evidence of a dose dependent relation within the recommended dose range of 1000 to 3000 mg/day, but incidence and severity of the central nervous system related undesirable effects decreased over time (Summary of product characteristics, Keppra, UK, 2006). Patients receiving Levetiracetam also reported a slightly higher incidence of symptoms of upper respiratory infection, which was not associated with leucopenia or dose reduction.

### 2.15.4 Drug Interactions -

Levetiracetam does not induce or inhibit hepatic biotransformation pathways (CYP isoforms, epoxide hydroxylase, or uridine diphosphate [UDP]-glucuronidation), nor is it significantly metabolized or protein bound.

Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam does not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products do not influence the pharmacokinetics of levetiracetam.
In clinical studies, plasma levels of concomitant AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, primidone, and valproate) were not changed by the addition of levetiracetam. As in adults, there is no evidence of clinically significant medicinal product interactions in pediatric patients receiving up to 60mg/kg/day levetiracetam.

The results of other studies in which levetiracetam was combined with digoxin, oral contraceptives, or warfarin indicate that the pharmacokinetics of either drug remain unaltered. By blocking tubular secretion, coadministration of probenecid is capable of reducing the renal clearance of levetiracetam's inactive metabolite (ucb L057) by 60%; however, the elimination of levetiracetam is unaffected. Therefore, this interaction is likely to be of little clinical significance.

No data on the influence of antacids on the absorption of levetiracetam or interaction of levetiracetam with alcohol are available [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].

2.15.5 Overdosage -

Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Somnolence, agitation, aggression, depressed level of consciousness; respiratory depression and coma were also observed in some cases. There is no specific antidote for overdose with levetiracetam. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient’s clinical status. In case of acute overdosage, gastric lavage haemodialysis may be required [ABPI Compendium Sheet, KEPPRA (Levetiracetam). UCB Pharma Limited. UK, August 2006].

2.16 Levetiracetam Pharmacokinetic-Pharmacodynamic considerations

2.16.1 Relationship between Levetiracetam plasma-concentration and therapeutic effects -

The relationship between Levetiracetam plasma-concentration and therapeutic effects has not been extensively described. However, one study objectively quantified the significant correlation between the anticonvulsant effects of levetiracetam in focal epilepsies and the peak serum concentration of the drug. (Stefan et al, 2006).

2.16.2 Relationship between Levetiracetam plasma-concentration and adverse effects -

No information is available on the Levetiracetam plasma-concentration and adverse effects relationship. However, the frequently occurring adverse events like somnolence, vertigo and dizziness appeared to be dose dependent [US Prescribing Information, KEPPRA (Levetiracetam), UCB, Inc, 2012].
2.17 Extended release formulation of Levetiracetam as adjuvant therapy in controlling partial-onset seizures

By controlling the rate of drug release, and hence absorption, extended release preparations aim to provide close to constant concentrations over a prolonged period of time.

Levetiracetam appears to target sites previously not involved in anticonvulsive therapy, including high-voltage calcium channels and the SV2A receptor. These new mechanisms of action may contribute to Levetiracetam’s low incidence of drug–drug interactions, making it especially useful in cases of refractory epilepsy in which polypharmacy often leads to increased adverse events.

An ideal antiepileptic drug is one that is efficacious in controlling seizures with no adverse events. The pharmacokinetic characteristics of this ideal AED would include: rapid absorption, good bioavailability, rapid achievement of steady-state concentrations, linear kinetics, minimal protein binding, absence of significant drug–drug interactions, a halflife allowing daily or bid dosing, a wide therapeutic index, and no metabolism (Patsalos, 2004).

Levetiracetam XR exhibits many of these ideal characteristics. It is rapidly and almost completely absorbed after oral ingestion, is 10% protein-bound, demonstrates linear kinetics, is minimally metabolized via a pathway independent of the cytochrome P450 system, has no active metabolites, has no significant drug–drug interactions, allows for once daily dosing, and has a wide therapeutic index.

Levetiracetam XR is ideal for patients with multiple medical problems on polytherapy and those with hepatic impairment. In addition, preliminary data suggest that Levetiracetam is a good AED option for patients on chemotherapeutic agents (Lim et al, 2009 and Wagner et al, 2003). However, given that Levetiracetam is renally excreted, dose adjustments are needed in patients with renal impairment and in some elderly patients due to an age-related decrease in creatinine clearance.

The efficacy, safety, and tolerability of Levetiracetam for the adjunctive treatment of partial-onset seizures have been clearly proven. Additional studies have suggested efficacy of Levetiracetam IR in the treatment of idiopathic generalized epilepsies and as monotherapy. Levetiracetam XR was well-tolerated in its pivotal trial. The most common adverse events reported were somnolence, irritability, dizziness, nausea, influenza, and nasopharyngitis. In addition, Levetiracetam does not alter body weight (Gidal et al, 2003), which may be a favorable characteristic. The most concerning associated adverse events are behavioral in nature and include agitation, anxiety, depression, nervousness, irritability and, rarely, psychosis. Those with learning disabilities and with a previous history of psychiatric illness may be at higher risk. Behavioral adverse events are reversible with discontinuation of levetiracetam (Safdieh and Harden, 2006).
One of the possible benefits of Levetiracetam XR is its once-daily dosing schedule because once and twice daily dosing have been shown to result in a higher rate of compliance, and there appears to be an inverse relationship between the number of daily medication doses and compliance (Claxton et al, 2001 and Pullar et al, 1988). Furthermore, because of relatively constant plasma concentrations, extended release formulations may minimize concentration-related adverse effects. These benefits should be weighed against the potential higher risk of a breakthrough seizure if a dose of a once-daily medication is missed, as the impact of a missed dose is greater the larger the dose and the less frequent the administration schedule (Bialer, 2007).

In short, an extended release formulation of Levetiracetam is expected to produce constant blood concentrations over the prolonged period with little or no fluctuations. Extended release formulation of Levetiracetam might improve the effectiveness and minimize the incidence of concentration related adverse events, thereby leading to ‘Improved Efficacy and Safety’.

2.18 Extended-release antiepileptic drugs: A comparison of pharmacokinetic parameters relative to original immediate-release formulations

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. Available ER formulations have the potential to minimize the spikes in maximum plasma concentrations ($C_{max}$) at steady-state that often contribute to AEs during treatment with immediate-release (IR) products. 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 (e.g., carbamazepine, divalproate sodium, lamotrigine, oxcarbazepine, levetiracetam, and phenytoin) have found that dose-normalized ER formulations may or may not be bioequivalent to their IR counterparts, but most ER formulations have a lower fluctuation index ($[C_{max} - C_{min}] / C_{avg}$) compared with the IR versions. This results in flatter concentration-time plots. Not all ER preparations improve the various PK parameters to the same
extent, and PK nuances may impact the effectiveness, tolerability, and adherence rates of various ER formulations (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).

2.19 BA and BE Studies for Orally Administered Drug Products

Bioavailability (BA) is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalence (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [US Food and Drug Administration's Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, 2003].

In Bioequivalence (BE) studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product (RLD). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product.

BE studies are a critical component of ANDA (Abbreviated New Drug Applications) submissions. The purpose of these studies is to demonstrate BE between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug. Together with the determination of pharmaceutical equivalence, establishing BE allows a regulatory conclusion of therapeutic equivalence.