

# Retigabine – A Promising New Antiepileptic Drug with a Novel Mechanism of Action

a report by

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Epilepsy affects up to 1% of the world's population. It is not a singular disease, but a variety of disorders reflecting underlying brain dysfunction that may result from myriad causes. The latest proposal by the International League Against Epilepsy (ILAE) defines epilepsy as the occurrence of at least one seizure with an enduring alteration in the brain structure or function, which increases the likelihood of future seizures.<sup>1</sup> An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal, excessive and synchronous neuronal activity in the brain. Depending on the pattern of neuronal involvement, the symptomatology (or semiology) of a seizure may consist of a wide range of sudden and transitory phenomena, which may include alterations of consciousness or motor, sensory, autonomic and psychic events. Based on the semiology and corresponding electroencephalographic and brain imaging changes, seizures can be broadly classified into partial (originating from a focal area of the cortex) and generalised (widespread involvement of bilateral cortical regions at the outset). Over the last decade, considerable advances have been made in our understanding of the molecular biology underlying seizure generation and propagation.<sup>2</sup> These have been accompanied by the licensing of a range of new antiepileptic drugs (AEDs).<sup>3</sup> However, despite these efforts, up to a third of patients continue to have seizures or intolerable side effects, and thus can be considered to have refractory epilepsy.<sup>4</sup> Uncontrolled seizures are associated with increased morbidity and mortality, posing a large economic burden on individuals and society. There continues, therefore, to be a need to develop more AEDs with novel mechanisms of action.<sup>5</sup>

## Pharmacology

Voltage-gated ion channels generate and control much of the electrical activity of neurons.<sup>6</sup> Inward currents are mediated by Na<sup>+</sup> and Ca<sup>++</sup> channels. Blockers of these channels represent important classes of AEDs and include phenytoin, carbamazepine, lamotrigine, oxcarbazepine, gabapentin and pregabalin. Examples of AEDs with other mechanisms of

action include those influencing gamma-aminobutyric acid (GABA) (e.g. sodium valproate, vigabatrin, tiagabine) and glutamate (e.g. topiramate, felbamate) neurotransmission. Levetiracetam binds to synaptic vesicle protein (SV2A) and may alter neurotransmitter trafficking by an as yet unknown mechanism.

## Potassium Channels

As a counterbalance to the role of Na<sup>+</sup> and Ca<sup>++</sup> channels in generating action potentials, K<sup>+</sup> channels serve as 'brakes' that limit neuronal excitability. M-current is a slowly activating, low-threshold K<sup>+</sup>-mediated flux that repolarises the neuronal membrane and controls the generation and frequency of the action potential.<sup>7</sup> M-current is largely mediated through KCNQ2 (Kv7.2) and KCNQ3 (Kv7.3) channels, which are expressed only on neurons. The fact that mutations in genes coding for these channels have been linked to neuronal hyperexcitability in infants with benign familial neonatal convulsions demonstrates the critical role that Kv7.2 and Kv7.3 channels play in regulating neuronal excitability.<sup>8,9</sup> Agents that activate or prolong opening of these M-current channels and thereby enhance the membrane's inherent 'braking' ability could be effective in disorders of neuronal hyperexcitability, such as epilepsy.

## Retigabine

Retigabine – N-(2-amino-4-(4-fluorobenzylamino)-phenyl)-carbamic acid ethyl ester – is a low-molecular-weight drug that was originally synthesised by Asta Medica in Germany and is currently undergoing phase III clinical development by Valeant Pharmaceuticals International as an adjunctive treatment for partial-onset seizures.<sup>10</sup> Its antiepileptic properties are largely due to its ability to activate and prolong the opening of neuronal potassium KCNQ2 (Kv7.2) and KCNQ3 (Kv7.3) channels.<sup>11</sup> In addition, retigabine potentiates GABA-evoked currents in cortical neurons via activation of GABA<sub>A</sub> receptors containing β2 or β3 subunits. The drug also blocks 4-aminopyridine-induced neosynthesis of neuroactive amino acids and stimulates *de novo* synthesis of GABA in hippocampal slices.<sup>12</sup> Retigabine has activity across a broad range of animal models of epilepsy, including maximal electroshock, pentylenetetrazole-induced seizures, many chemoconvulsant models, amygdala kindling and some genetic models (DBA/J2 mice and GEPR rats) of epilepsy.<sup>13</sup> The drug displays activity in several animal models of drug-resistant epilepsy.<sup>14</sup> Administered intraperitoneally, retigabine is active in the rodent cobalt-homocysteine thiolactone model of status epilepticus.<sup>13</sup> In addition, it has been shown to suppress spontaneous and induced discharges in human cortical tissue excised from patients undergoing epilepsy surgery.<sup>15</sup>

## Pharmacokinetics

Retigabine is rapidly absorbed following oral intake, with 60% bioavailability.<sup>16</sup> Plasma protein binding is not high at 80%. Its pharmacokinetics are linear and dose-proportional with an elimination half-



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life approximating eight hours.<sup>17</sup> The drug is not a substrate for the cytochrome P450 enzyme superfamily. Most of retigabine's metabolism is via phase II hepatic glucuronidation and N-acetylation resulting in the production of the pharmacologically active metabolite, N-acetyretigabine.<sup>18</sup> Two recent studies have shown that different genotypes of N-acetyltransferase (NAT)<sup>19</sup> or UDP-glucuronyltransferase (UGT)<sup>20</sup> do not have a clinically significant effect on the human clearance of retigabine. There are no clinically relevant interactions between retigabine and phenobarbital, valproic acid or topiramate.<sup>21</sup> Its plasma clearance is induced by phenytoin and carbamazepine, although retigabine itself does not affect the pharmacokinetics of either of these drugs.<sup>21</sup> Lamotrigine exerts a modest effect on retigabine clearance, resulting in higher drug exposure, although this is unlikely to be clinically relevant.<sup>22</sup> Retigabine does not influence the pharmacokinetics of the hormonal components (ethinylestradiol and norgestrel) of the oral contraceptive pill.<sup>23</sup>

### Randomised Trials

The safety and efficacy of retigabine has been evaluated in five phase II studies involving almost 600 patients with refractory epilepsy. The largest included 399 patients aged 18–70 years with uncontrolled partial-onset seizures with or without secondary generalisation.<sup>24</sup> Patients were randomised in a double-blind fashion to placebo or one of three doses of retigabine – 600, 900 or 1200mg/day. All participants reaching the end of titration entered an eight-week maintenance period during which their retigabine dose was held constant. The primary analysis was carried out on the intent-to-treat population and seizure frequency over the total 16-week double-blind period was compared with that in the eight-week baseline. Of the 399 randomised patients, 279 (70%) completed the double-blind treatment period. The median percentage reduction in monthly partial seizure frequency was 23% in the 600mg retigabine group, 29% in the 900mg group and 35% in the 1200mg group compared with 13% in patients randomised to placebo. A dose–response relationship was observed across the treatment arms ( $p < 0.001$ ). Both the 900mg and 1200mg daily groups proved superior to placebo and 1200mg retigabine was superior to the 600mg group. Responder rates (50% reduction in monthly seizure frequency from baseline) for retigabine were 23% for the 600mg group, 32% for the 900mg group and 33% in the 1200mg group compared with 16% in placebo-treated patients. Statistical analysis of responder rates yielded similar results to those noted above for overall

seizure reduction. Among the 222 patients who were enrolled into the open-label extension, the median duration of treatment was almost one year and the reduction in seizure frequency observed during the double-blind study appeared to be durable over a longer treatment period.<sup>25</sup>

### Adverse Events

The most common treatment-emergent adverse events in the published randomised trial were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, memory difficulty, abnormal thinking, abnormal gait, paraesthesia and diplopia.<sup>24</sup> A total of 79 patients withdrew due to adverse events: 12 patients (12.5%) in the placebo group; 17 patients (17%) in the 600mg retigabine group; 19 patients (20%) in the 900mg group; and 31 patients (29.2%) in the 1200mg group. Most of the discontinuations occurred during the titration period. No clinically relevant effects were noted on the electrocardiogram or in routine haematological and biochemical testing. There was a slight overall increase in bodyweight (2–3%) in the 1200mg retigabine treatment group, but no subject withdrew from the study due to weight gain.

### Current Studies

The phase III programme for the development of retigabine as an adjunctive treatment for partial seizures has been designated as the Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy (RESTORE) programme and consists of two independent but complementary randomised, placebo-controlled, double-blind studies undertaken in the US and Europe. Both were designed according to regulatory standards with the guidance of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These trials are due to complete in 2008.

### Conclusion

Retigabine has a novel molecular target compared with currently available and investigational AEDs. Its activation of neuron-specific potassium channels enhances the 'braking' function of neuronal stabilisation. The drug has been shown to be safe and effective in a well-controlled dose–response study in patients with refractory localisation-related epilepsy. Longer-term open-label studies have confirmed its efficacy. The phase III trial programme will complete early next year. When approved, retigabine will be an important addition to the therapeutic armamentarium for the treatment of patients with refractory epilepsy. ■

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