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## BRIVARACETAM (UCB 34714) UPDATE

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Brivaracetam (ucb 34714) is a novel high-affinity synaptic vesicle protein 2A (SV2A) ligand and also has inhibitory activity at neuronal voltage-dependent sodium channels. Currently brivaracetam is in phase III development for epilepsy.

The activity profile of brivaracetam in a wide range of animal models of epilepsy suggests potential broad spectrum activity with a potency and efficacy superior to levetiracetam.

Brivaracetam is completely absorbed, weakly bound to plasma proteins (.20%), extensively metabolised and eliminated renally. It has linear pharmacokinetics and a plasma half-life of ~8 hours. Monitoring of plasma concentrations of concomitant antiepileptic drugs (AEDs) during phase II/III trials indicated that no dose adjustment would be required when adding brivaracetam to other AEDs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate or zonisamide), although carbamazepine epoxide was increased moderately when high doses of brivaracetam are added to patients who are on high doses of carbamazepine.

Two phase III, randomized, double-blind, placebo-controlled, fixed-dose, 12-week trials enrolled adults (16.70 years) with focal epilepsy inadequately controlled with 1.2 concomitant AEDs. In study N01253, patients received brivaracetam 5 (n=97), 20 (n=100), 50 (n=101) mg/day or placebo (n=98) b.i.d., without titration. In study N01252, patients received brivaracetam 20 (n=99), 50 (n=99) or 100 (n=100) mg/day or placebo (n=100) b.i.d., without titration. In both studies, the primary efficacy variable was the partial-onset seizure (POS) frequency/week over the 12-week treatment period. Multiplicity was controlled by comparing each brivaracetam arm to placebo in a pre-defined order starting with brivaracetam 50 mg/day for both studies.

Study N01253 achieved statistical significance on the primary efficacy endpoint of percent reduction over placebo ( $p=0.025$  for 50 mg/day). Study N01252 did not achieve statistical significance on the primary efficacy endpoint ( $p=0.261$  for 50 mg/day); however, statistical significance was achieved for brivaracetam 100 mg/day at the nominal 0.05 level ( $p=0.037$ ).

Secondary efficacy analyses provided supportive evidence for the efficacy of brivaracetam 50 mg/day (N01253) and 100 mg/day (N01252). The 50% responder rates versus placebo (brivaracetam/placebo) were statistically significantly higher for brivaracetam 50 mg/day (32.7%/16.7%;  $p=0.008$ ; N01253) and 100 mg/day (36.0%/20.0%;  $p=0.023$ ; N01252). Median percent reductions from baseline in POS frequency/week versus placebo (brivaracetam/placebo) were statistically significantly higher for brivaracetam 50 mg/day (30.5%/17.8%;  $p=0.003$ ; N01253) and 100 mg/day (32.5%/17.0%;  $p=0.004$ ; N01252).

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Adjunctive brivaracetam demonstrated a favourable safety and tolerability profile in the phase IIb and III fixed-dose (5-150 mg/day) trials in patients with focal epilepsy as well as in a flexible-dose (20-150 mg/day) phase III trial in patients with focal or primary generalized epilepsy. Across all phase IIb/III trials, overall discontinuation rates and discontinuation rates due to treatment-emergent adverse events (TEAEs) in brivaracetam groups were low and similar to placebo. The most common TEAEs were headache, somnolence, dizziness and fatigue.

A new phase III, randomized, double-blind, placebo-controlled, fixed-dose study in adults with focal epilepsy inadequately controlled with 1-2 concomitant AEDs has been recently initiated to evaluate efficacy and safety of brivaracetam 100 mg/day and 200 mg/day as adjunctive treatment.