

GANAXOLONE: Neurosteroid Therapy For Epilepsy

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Ganaxolone (3-hydroxy-3-methyl-5-pregnan-20-one) is a new chemical entity in development for the treatment of epilepsy. It is a neuroactive steroid which allosterically modulates -aminobutyric acid type A (GABAA) receptors in the central nervous system (CNS). Ganaxolone affects GABAA receptors by interacting with a recognition site that is distinct from other allosteric GABAA receptor modulators, including benzodiazepines, and barbiturates. Chemically, ganaxolone is the 3-methyl analog of the progesterone metabolite allopregnanolone (3-hydroxy-5-pregnan-20-one; 5,3-P).

Allopregnanolone exhibits potent antiepileptic, anxiolytic, sedative, and hypnotic activities in animals by virtue of its GABAA receptor modulating activity. Ganaxolone has similar pharmacological actions on GABAA receptors as 5,3-P and it also has potent protective activity against seizures in animal models but in contrast to allopregnanolone, ganaxolone cannot be converted in the body to 3-keto intermediates with classical steroid hormone activity.

Data from nonclinical studies indicate that ganaxolone is a high-affinity, stereoselective, positive allosteric modulator of the GABAA receptor complex that exhibits potent anticonvulsant activity in animal models at doses that do not cause ataxia or cognitive impairment. Nonclinical studies further suggest that ganaxolone has a reduced propensity for interaction with ethanol than valproate, barbiturates and benzodiazepines. The profile of anticonvulsant activity obtained for ganaxolone in antiepileptic drug screening models supports clinical evaluation as an antiepileptic therapy with potential utility in the treatment of simple and complex partial seizures. Toxicology studies to date show little evidence for target organ or systemic toxicity, and ganaxolone was not teratogenic in rats or mice. No potential for mutagenicity or carcinogenicity has been detected.

In a completed Phase 2a clinical study in adults with partial seizures (N=146), ganaxolone at 1500mg/day was shown to be safe, efficacious and well-tolerated. Onset of efficacy was noted within the first week, and at endpoint, ganaxolone-treated subjects had significantly greater reduction in mean weekly seizure frequency than subjects treated with placebo. Ganaxolone was well tolerated, with only dizziness, fatigue and somnolence occurring in more than 5% of subjects and at twice the rate of placebo or more. To date, over 900 human subjects have been exposed to ganaxolone, including children and infants 6 mo to 1 year old.

Marinus Pharmaceuticals, Inc. licensed ganaxolone from Purdue Pharma, LP and has invented an improved oral formulation with strong IP position. Research also continues on a solid dose formulation.

In summary, ganaxolone is the first neurosteroid to successfully complete a Phase 2 study demonstrating efficacy, safety and tolerability in treatment of epilepsy. Additional investigations into psychiatric indications are also under consideration.