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Ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one) is a new chemical entity under investigation for use as an antiepileptic drug. It is a neuroactive steroid that allosterically modulates γ -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, non-benzodiazepines and barbiturates. Chemically, ganaxolone is the 3 β -methyl analog of the progesterone metabolite allopregnanolone (3 α -hydroxy-5 α -pregnan-20-one; 5 α ,3 α -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 α ,3 α -P and it also has potent protective activity against seizures in animal models, but in contrast to allopregnanolone it 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 impairing cognitive function and for interacting 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. Further, reports have indicated that antiepileptic drugs with GABAA receptor positive modulating activity, including benzodiazepines and topiramate, may have efficacy in the treatment of infantile spasms, supporting the evaluation of ganaxolone in this condition.

To date, over 500 patients and 200 normal volunteers have been exposed to ganaxolone. In the epilepsy clinical development program, 24 adult patients received up to 10 days of monotherapy with ganaxolone in a double-blind inpatient clinical study. Patients on drug exited the trial later than those on placebo, though the study did not reach statistical significance. Seventy-nine pediatric patients were treated in five open-label clinical studies designed to assess the safety, tolerability, and potential efficacy of ganaxolone in the treatment of seizures refractory to conventional therapies. Anecdotal evidence of seizure improvement was seen in these studies.

Marinus Pharmaceuticals, Inc. licensed ganaxolone from Purdue Pharma, LP and is continuing clinical development. New formulation work has generated a strong IP position as well as allowing for Phase II studies in Infantile Spasms and Refractory Partial Onset Seizures to be conducted. The study in adults will evaluate the effect of ganaxolone on catamenial seizures. These trials, which were initiated in 2007, are both ongoing and scheduled to complete this year. Further work on a solid dose formulation is also underway.

In summary, ganaxolone is a neuroactive steroid with anticonvulsant activity now in Phase II testing with a new formulation. Areas of potential differentiation include therapy for Infantile Spasms and catamenial seizures. Development in other indications is also being considered.