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Tonabersat

H. Steve White, Ph.D.
Anticonvulsant Drug Development Program
University of Utah
Salt Lake City, UT

Tonabersat is a novel benzoylamino benzopyran compound that has shown promise as a mechanistically novel investigational antiepileptic drug (AED) in early development for the treatment of partial seizures. Tonabersat selectively inhibits Connexin 26-mediated neuronal gap junction communication; an action that is thought to contribute to its ability to modulate cortical spreading depression and normalize trigeminal neuron sensitization. Tonabersat does not display any activity in other receptor or enzyme assays. The extent to which this stereoselective action of tonabersat contributes to its anticonvulsant action is not yet known.

In rodent seizure models, tonabersat blocks tonic extension seizures induced by threshold and supra-maximal electroshock corneal stimulation, as well as tonic extension seizures induced by pentylenetetrazol (PTZ). Tonabersat also blocks audiogenic seizures (AGS) in the Frings AGS-susceptible mouse model of reflex epilepsy. Tonabersat does not modify myoclonic seizures or lower seizure threshold. Tonabersat's preclinical profile suggests that it would be useful for the treatment of human generalized tonic-clonic seizures and partial onset seizures with or without secondary generalized tonic clonic seizures.

In addition to its anticonvulsant activity, tonabersat has shown activity in a variety of preclinical models of migraine; e.g., tonabersat inhibits chemically induced repetitive cortical spreading depression and associated NO release. It also blocks trigeminal sensory nerve stimulation evoked inflammation and neurovascular reflexes.

In vitro metabolism studies suggest that tonabersat possesses a moderate liability for drug-drug interaction; i.e., it displayed strong *in vitro* inhibition of human CYPs 2D6, 2C9, 2C19; moderate inhibition of 3A4 and 2B6 and weak inhibition of 1A2 and 2A6.

Results from human Phase 1 studies suggest that tonabersat is generally well tolerated at doses of 80, 160 and 200mg QD for 14 days in normal volunteers. Dizziness was the most commonly reported AE, followed by fatigue, nausea, headache and somnolence. Dizziness was reported by a higher proportion of subjects receiving the two highest doses (160-200mg). Moreover, tonabersat displays linear pK with a mean T_{1/2} of 32 hrs. The rate, but not extent, of absorption is affected by food.

Overall, tonabersat represents a mechanistically novel antiepileptic drug that shows activity in animal models of partial seizures, generalized tonic-clonic seizures, and migraine, with favorable pharmacokinetic properties. Ongoing preclinical and clinical studies will evaluate tonabersat's liability for drug-drug interactions that are suggested by *in vitro* drug metabolizing studies. Results from early clinical studies suggest that tonabersat is likely to be well tolerated and supports further clinical evaluation.