Currently available anti-epileptic drugs do not solely affect glutamatergic transmission. Their mechanism of action is generally conceptualized as altering the balance between excitatory (glutamate-mediated) and inhibitory (GABA-mediated) transmission (Johannessen Landmark "Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy" CNS Drugs 2008, Vol. 22(1), pp. 27-47).

A significant limiting factor in the use of SV2A ligands is tolerability and side-effect profile. For example the effective dose of levetiracetam for partial onset seizures is dosed at 1000 mg, 2000 mg, and 3000 mg, given as twice-daily. The side effects reported for levetiracetam include aggressive or angry behavior, anxiety, change in personality, chills, cough or hoarseness, crying, depersonalization, diarrhea, dry mouth, euphoria, fever, general feeling of discomfort or illness, headache, hyperventilation, irregular heartbeats, irritability, joint pain, loss of appetite, lower back or side pain, mental depression, muscle aches and pains, nausea, painful or difficult urination, paranoia, quick to react or overreact emotionally, rapidly changing moods, restlessness, shaking, shivering, shortness of breath, sleepiness or unusual drowsiness, sore throat, stuffy or runny nose, sweating, trouble sleeping, unusual tiredness or weakness and vomiting. Thus, there is still a need to provide an effective treatment with a lower effective dose of levetiracetam and a more favourable side effect profile for the treatment of epilepsy and related disorders, not only in the adult but also in the pediatric population.

SUMMARY

In one aspect, there is provided a combination comprising (a) a synaptic vesicle protein 2A ("SV2A") ligand; and (b) a positive allosteric modulator ("PAM") of metabotropic glutamatergic receptor subtype 2 ("mGluR2") compound or a pharmaceutically acceptable salt or a solvate thereof, or an orthosteric agonist of metabotropic glutamatergic receptor subtype 2 compound or a pharmaceutically acceptable salt or a solvate thereof.

In another aspect, there is provided a pharmaceutical composition comprising a combination as claimed in any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

In another aspect, there is provided a process for the preparation of the pharmaceutical composition according to claim 13, wherein the combination as claimed in any one of claims 1 to 12 is intimately admixed with a pharmaceutical carrier.

In another aspect, there is provided a product comprising the combination of the SV2A ligand and the compound of Formula (I), as defined in any one of claims 1 to 12, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; bipolar and related disorders.

In another aspect, there is provided a combination as defined in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, for use as a medicament.

In another aspect, there is provided a combination as claimed in any one of claims 1 to 12 for use in neuroprotection.

In another aspect, there is provided a combination as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, for use in the prevention of epileptogenesis.

In another aspect, there is provided use of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament for the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; and bipolar and related disorders.

In another aspect, there is provided use of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament for neuroprotection.

In another aspect, there is provided use of a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament for anti-epileptogenesis.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Dose response for the 6Hz 44mA ED_{50} determination for the Co. No. **2** and LEV alone and in combination.

Figure 2: Isobolographic analysis for the combination of Co. No. **1** with levetiracetam (LEV) in the 6Hz (44 mA) assay. Initial ED_{50} values (shown below) were determined for both Co. No. **1** and LEV (data points on x- and y-axes; filled diamonds). The theoretical line of additivity connects the calculated ED_{50} values for the two compounds (solid black line). Theoretical ED_{50} (+ SEM) for three fixed dose ratio combinations (LEV: Co. No. **1**) are plotted: 1:3 – filled squares/solid black line, 1:1 – filled upward triangles/solid black line, and 3:1 – filled downward triangles/solid black line. Experimental treatment doses were initially derived from theoretical values and adjusted according to observed effects. Experimentally-determined ED_{50} (+ SEM)

18. A combination as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, for use in the prevention of epileptogenesis.

19. Use of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament ~~A method~~ for the treatment or prevention of epilepsy and related disorders; neuropathic pain; migraine or resistant headache; and bipolar and related disorders~~; said method comprising administering a therapeutically effective amount of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, to a subject in need thereof~~.

20. Use of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament for ~~A method of~~ neuroprotection~~, said method comprising administering a therapeutically effective amount of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, to a subject in need thereof~~.

21. Use of a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13 in the manufacture of a medicament for ~~A method of~~ anti-epileptogenesis~~, said method comprising administering a therapeutically effective amount of a combination or a combination product as claimed in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 13, to a subject in need thereof~~.