METHODS OF TREATING EPILEPSY OR STATUS EPILEPTICUS

Claims of Priority

This application claims priority to U.S.S.N. 61/691,545, filed August 21, 2012 and U.S.S.N. 61/789,491, filed March 15, 2013, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present invention generally relates to methods of treating epilepsy or status epilepticus by administering a neuroactive steroid.

Summary

In one aspect, the present disclosure refers to a method of preparing a formulation comprising allopregnanolone, said method comprising the step of high shear mixing an aqueous solution comprising 5 mg/mL allopregnanolone and 25% sulfo butyl ether beta-cyclodextrin for a time period of one hour.

Described herein are methods of treating epilepsy or status epilepticus.*e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.,* generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; periodic lateralized epileptiform discharges; a seizure, *e.g.,* acute repetitive seizures, cluster seizures, the method comprising administering to the subject a neuroactive steroid. In one example, the present disclosure features a method of treating a subject having epilepsy or status epilepticus by administering in combination to the subject a neuroative steroid and a benzodiazepine. In some examples, the method further comprises administering at least one of the neuroative steroid or benzodiazepine parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some examples, both the neuroative steroid and benzodiazepine are administered parenterally.

In some examples, the neuroative steroid and benzodiazepine are co-administered (*e.g.,* administered simultaneously). In some examples, the neuroative steroid and benzodiazepine are administered sequentially. In some examples, neuroative steroid and benzodiazepine are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a in the absence of the combination regimen. The agents may be administered separately, as part of a multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this disclosure in a single composition.

In some examples, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone. In an example, the neuroactive steroid is allopregnanolone.

In some examples, the neruroactive steroid, *e.g.,* alloprenanolone, is formulated for parenteral administration (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, the neneuroactive steroid, *e.g.,* allopregnanolone, is administered in a composition comprising a cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex. a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®.

In some examples, the cyclodextrin is a β-cyclodextrin. In an example, the cyclodextrin is a sulfo butyl ether β-cyclodextrin. In an example, the cyclodextrin is CAPTISOL®. In some examples, the cyclodextrin is a β-cyclodextrin disclosed in U.S. Patent Nos. 5,874,418; 6,046,177; or 7,635,733, which are herein incorporated by reference.

In some examples, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone, and the cyclodextrin is a β-cyclodextrin. In an example, the neuroactive steroid is allopregnanolone and the cyclodextrin is CAPTISOL®.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated for parenteral administration. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration between 0.25-30mg/mL, 0.5-30mg/mL; 1-30mg/mL; 5-

30mg/mL, 10-30mg/mL; 15-30mg/mL, 0.25-20mg/mL; 0.5-20mg/mL; 1-20mg/mL, 0.5-20mg/mL; 1-20mg/mL, 5-20mg/mL, 10-20mg/mL, 0.25-15mg/mL, 0.5-15mg/mL; 0.5-10mg/mL; 1-15mg/mL, 1-10mg/mL; 1-5mg/mL; 5-15mg/mL; 5-10mg/mL; 10-15mg/mL; 1-10mg/mL; 2-8mg/mL; 2-7mg/mL; 3-5mg/mL; 5-15mg/mL; 7-12mg/mL; 7-10mg/mL; 8-9mg/mL; 3-5mg/mL; or 3-4mg/mL.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 0.25mg/mL, 0.5mg/mL; 1.0mg/mL; 1.5mg/mL; 2.0mg/mL; 2.5mg/mL; 3.0mg/mL; 3.5mg/mL; 4.0mg/mL; 4.5mg/mL; 5.0mg/mL, 5.5mg/mL, 6.0mg/mL, 6.5mg/mL, 7.0mg/mL, 7.5mg/mL, 8.0mg/mL, 8.5mg/mL, 9.0mg/mL, 9.5mg/mL, 10mg/mL, 15mg/mL, 20mg/mL, 25mg.mL, or 30 mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 1.5mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 5mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 15mg/mL.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration between 25-400mg/mL; 25-300mg/mL; 25-200mg/mL; 25-100mg/mL; 25-50mg/mL; 50-400mg/mL; 50-300mg/mL; 60-400mg/mL; 60-300mg/mL; 150-400mg/mL; 150-300mg/mL; 200-300mg/mL; 200-400mg/mL; 30-100mg/mL; 300-400mg/mL; 30-100mg/mL; 45-75mg/mL; 50-70mg/mL; 55-65mg/mL; or 50-60mg/mL. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 25mg/mL; 30mg/mL; 35mg/mL; 40mg/mL; 45mg/mL; 50mg/mL; 55mg/mL; 60mg/mL; 65mg/mL; 70mg/mL; 75mg/mL; 80mg/mL; 85mg/mL;

90mg/mL, 95mg/mL; 100mg/mL; 150mg/mL; 200mg/mL; 250mg/mL; 300mg/mL; 350mg/mL; or 400mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 60mg/ml. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising between 2.5-40%, 2.5-30%, 2.5-20%, 2.5-10%, 5-40%, 5-30%, 5-20%, 5-10%, 6-40%, 6-30%, 6-20%, 6-10%, 10-40%, 10-30%, 10-20%, 20-40%, 20-30%, 25-40%, 25-30%, 3-10%, 4.5-7.5%, 5-7%, 5.5-6.5% of the cyclodextrin, *e.g.,* CAPTISOL®. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 2.5%, 3%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% of the cyclodextrin, *e.g.,* CAPTISOL®. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 6% of the cyclodextrin. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 15% of the cyclodextrin. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 30% of the cyclodextrin.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH between 3-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-9, 5-8, 5-7, 5-6, 4.5-7.5, or 5.5-7.5. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, or 9. In an example, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 6.

In an example, a composition comprising a neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex, comprises less than 100ppm of

a phosphate, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 300 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to a color forming agent, as determined by UV/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 20 ppm of a sulfoalkylating agent; less than 0.5% wt. of an underivatized cyclodextrin; less than 1% wt. of an alkali metal halide salt; and less than 0.25% wt. of a hydrolyzed sulfoalkylating agent.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 50 ppm of a phosphate; less than 10 ppm of a sulfoalkylating agent; less than 0.2% wt. of an underivatized cyclodextrin; less than 0.5% wt. of an alkali metal halide salt; and less than 0.1% wt. of a hydrolyzed sulfoalkylating agent; and wherein the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether

β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to the color-forming agent, as determined by U/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 10 ppm of a phosphate; less than 2 ppm of a sulfoalkylating agent; less than 0.1% wt. of an underivatized cyclodextrin; less than 0.2% wt. of an alkali metal halide salt; and less than 0.08% wt. of a hydrolyzed sulfoalkylating agent; and wherein the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.1 A.U. due to the color-forming agent, as determined by UV/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 5 ppm of a phosphate; less than 0.1% wt. of an alkali metal halide salt; and less than 0.05% wt. of a hydrolyzed sulfoalkylating agent.

In some examples, the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered within 10 hours, 8 hours, 5 hours, 3 hours, 1 hour, or 0.5 hour after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has started. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered within 60 minutes, 45 minutes, 30 minutes, 15 minutes, 10 minutes, or 5 minutes after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has started. In some examples, the the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has lasted 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes or 60 minutes.

In some examples, the the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered prior to the onset of a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure.

In some examples, the benzodiazepine is clonazepam, lorazepam, midazolam, or diazepam.

In some examples, the benzodiazepine is formulated for oral delivery. In some examples, the benzodiazepine is formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, both the neuroactive steroid and the benzodiazepine are formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination, are administered in an amount sufficient to achieve burst suppression (*e.g.,* a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM). In some examples, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination is administered at a dose sufficient to achieve a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds, 5-30 seconds, 10-30 seconds, 15-30 seconds, 1-30 seconds, 0-30 seconds, 2-20 seconds, 2-10 seconds, 5-20 seconds, 10-20 seconds, 15-25 seconds, 5-15 seconds or 5-10 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM.

In one example, the present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising: administering to said subject (*e.g.,* human subject), an effective amount of allopregnanolone, wherein, concurrent with said administering, said subject (*e.g.,* human subject) is under general anesthesia, thereby treating said subject (*e.g.,* human subject).

In one example, the present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising administering a first

dose, *e.g.,* a load dose, of allopregnanolone, *e.g.,* to a patient under general anesthesia; administering a second dose, *e.g.,* maintenance dose, of allopregnanolone, which is lower than said first dose; and administering a third dose, *e.g.,* a downward taper dose, of allopregnanolone, said allopregnanolone doses being sufficient to treat said subject (*e.g.,* human subject).

In some examples, said subject (*e.g.,* human subject) is not under general anesthesia for at least a portion of the second dose. In some examples, said subject (*e.g.,* human subject) is not under general anesthesia for at least a portion of the third dose. In some examples, said subject (*e.g.,* human subject) is under general anesthesia during the administration of the first dose and during administration of a portion of the second dose, *e.g.,* for at least, or up to, 6, 12, 24, or 47 hours of the second dose.

In some examples, the second dose is administered over a period of time that is at least 60, 65, 70, 80, 90, 100, 110, 120 times longer in duration than that of said first dose. In some examples, the second dose is administered over a period of time that not more than 80, 90, 100, 110, 120, 130, or 140 times longer in duration than that of said first dose.

In some examples, the second dose is administered over a period of time that at least 2, 3, 4, 5, 6 times longer in duration than that of said third dose. In some examples, the second dose is administered over a period of time that not more than 5, 6, 7, 8, 9, or 10 times longer in duration than that of said third dose.

In some examples, the infusion rate, *e.g.,* amount of allopregnanolone delivered/unit time in the second dose, *e.g.,* as measured in □g/kg/hour, is at least 2, 3, 4, 5, or 6 times lower than that of the first dose.

In some examples, one, two or all of said doses are injected, *e.g.,* IV administrations.

In some examples, said subject (*e.g.,* human subject) has failed to respond to a first line treatment, *e.g.,* a benzodiazepine (*e.g.* midazolam), *e.g.,* as evidenced by a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

In some examples, said subject (*e.g.,* human subject) has failed to respond to a second line treatment, *e.g.,* phenytoin, fos-phenytoin, valproate, phenobarbitol, or levetiracetam, *e.g.,* as evidenced by a

failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

In some examples, the method further comprises administering an amount of an aesthetic effective to place said subject (*e.g.,* human subject) under general anesthesia. In some examples, said anesthetic is selected from a benzodiazepine (e.g. midazolam), propofol, and pentobarbital.

In some examples, the method further comprises a weaning period in which said subject (*e.g.,* human subject) is weaned from said general anesthesia. In some examples, said weaning period is initiated during the administration of said second dose. In some examples, said weaning period is completed during the administration of said second dose. In some examples, said weaning period is initiated within 12, 24, 36, 48, 60 or 72 hours after initiation or completion of the first dose of allopregnanolone. In some examples, said weaning period is initiated at 48 hours after initiation or completion of the first dose of allopregnanolone. In some examples, said weaning period is 18 to 30 hours, 20 to 28 hours, or 22 to 26 hours in duration. In some examples, said weaning period is 24 hours in duration.

In some examples, the administration of allopregnanolone, *e.g.,* the first or load dose, is initiated within a preselected period of time, wherein said period begins with: the administration of said anesthetic; or the induction of general anesthesia. In some examples, said preselected period is not longer than 48, 24, 12, 6, 5, 4, 3, 2, or 1 hour. In some examples, said preselected period is not longer than 120, 60, 30, 15, or 5 minutes.

In some examples, said second dose is initiated while the subject (*e.g.,* human subject) is under general anesthesia. In some examples, the amount of allopregnanolone delivered per hour in said second dose is the same or lower than the amount delivered per hour in said first dose.

In some examples, the administration of the first dose of allopregnanolone is initiated within a preselected period of time, wherein said period begins with: the administration of said anesthetic or the induction of general anesthesia. In some examples, said preselected period is at least 6, 12, 24, 48 or 60 hours. In some examples, said preselected period is not longer than 24, 48, or 60 hours. In some examples, said preselected period is between 2 to 120, 2 to 60, 4 to 120, 4 to 60, 4 to 48, 4 to 36, or 4 to 24 hours. In some examples, said preselected period is not longer than 48, 24, 12, 6, 5, 4, 3, 2, or 1 hour. In some examples, said preselected period is not longer than 120, 60, 30, 15, or 5 minutes.

In some examples, said first dose is begun after failure of the subject (*e.g.,* human subject) to respond to prior treatment. In some examples, the failure to respond is evidenced by one or more of, a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording. In some examples, said prior treatment comprises administration of a first line treatment, *e.g.,* a benzodiazepine (e.g. midazolam). In some examples, said prior treatment comprises administration of a second line treatment, *e.g.,* phenytoin, fos-phenytoin, valproate, phenobarbitol, or levetiracetam.

In some examples, said first dose is a load, *e.g.,* bolus, dose. In some examples, said first dose results in a plasma concentration of 50 to 500 nM, 100 to 400 nM, or 200 to 300 nM. In some examples, said first dose results in a plasma concentration of 500 to 1000 nM, 600 to 900 nM, or 700 to 800 nM. In some examples, said first dose results in a plasma concentration of 1000 to 1500 nM, 1100 to 1400 nM, or 1200 to 1300 nM. In some examples, said first dose results in a plasma concentration of 1500 to 2000 nM, 1600 to 1900 nM, or 1700 to 1800 nM. In some examples, said first dose results in a plasma concentration of 2000 to 2500 nM, 2100 to 2400 nM, or 2200 to 2300 nM. In some examples, said first dose results in a plasma concentration of 300 to 800 nM, 400 to 700 nM, or 500 to 600 nM. In some examples, said first dose results in a plasma concentration of 800 to 1300 nM, 900 to 1200 nM, or 1000 to 1100 nM. In some examples, said first dose results in a plasma concentration of 1300 to 1800 nM, 1400 to 1700 nM, or 1500 to 1600 nM. In some examples, said first dose results in a plasma concentration of 1800 to 2300 nM, 1900 to 2200 nM, or 2000 to 2100 nM. In some examples, said first dose results in a plasma concentration of 2300 to 2600 nM, 2400 to 2500 nM. In some examples, said first dose results in a plasma concentration of 300 to 400 nM, 400 to 500 nM, 600 to 700 nM, 800 to 900 nM, 1100 to 1200 nM, 1300 to 1400 nM, 1400 to 1500 nM, 1600 to 1700 nM, 1800 to 1900 nM, 1900 to 2000 nM, 2100 to 2200 nM, 2300 to 2400 nM. In some examples, said first dose results in a plasma concentration of 500 to 2500 nM, 500 to 1500 nM, 500 to 1000 nM, 500 to 800, or 500 to 600, nM. In some examples, said first dose results in a plasma concentration of 50 to 250 nM, 100 to 200 nM, or 140 to 160 nM. In some examples, said first dose results in a plasma concentration of 150 +/- 30 nM, 150 +/- 20 nM, 150 +/- 10 nM, or 150 nM.

In some examples, the plasma concentration of said first dose is measured at a preselected time, *e.g.,* at 10, 15, 20, 30, 45, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said first dose.

In some examples, said first dose is administered over a period of time that is not longer than 6, 5, 4, 3, 2, or 1 hour. In some examples, said first dose is administered over a period of time that is at least 10, 20, 30, 40, 50, 60, 70, 80, or 90 minutes in duration. In some examples, said first dose is administered over a period of time that is 30 to 120 minutes, 45 to 100 minutes, or 50 to 70 minutes, in duration. In some examples, said first dose is administered over a period of time that is 60 +/- 15 minutes, 60 +/- 10 minutes, 60 +/- 5 minutes, or 60 minutes, in duration.

In some examples, said first dose is administered at a dosage rate of 200-3500 □g/kg/hour. In some examples, said first dose is administered at a dosage rate of 200-350 □g/kg/hour, 250-300 □g/kg/hour, 280-290 □g/kg/hour, 286 □g/kg/hour, 287 □g/kg/hour, or 288 □g/kg/hour, *e.g.,* for one hour.

In some examples, said second dose is a maintenance dose. In some examples, the administration said second dose is initiated within a preselected time period, wherein said time period begins with the administration of said anesthetic. In some examples, the administration said second dose is initiated within a preselected time period, wherein said time period begins with the induction of general anesthesia. In some examples, the administration said second dose is initiated within a preselected time period, wherein said time period begins with the beginning of the first dose. In some examples, the administration said second dose is initiated within a preselected time period, wherein said time period begins with the end of the first dose. In some examples, the administration said second dose is initiated within a preselected time period, wherein said time period begins with the achievement of a predetermined level of allopregnanolone, *e.g.,* in the plasma. In some examples, said time period begins with the end of the first dose. In some examples, said preselected time period begins with beginning or ending of the administration of the first dose and is not longer than 240, 180, 120, 60, 30, 15, or 5 minutes. In some examples, said preselected time period begins with beginning or ending of the administration of the first dose and is not longer than 90, 80, 70, or 60 minutes. In some examples, the administration of the second dose begins no longer than 90, 80, 70, 60, or 30 minutes after the beginning or end of the administration of the first dose. In some examples, the administration of the second dose begins 50 to 70, 55 to 65, or 60 minutes after the beginning or end of the administration of the first dose. In some examples,

the administration of the second dose begins no more than 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, 1 minute after the end of administration of the first dose. In some examples, the administration of the second dose begins at the end of administration of the first dose.

In some examples, the administration of the first dose and the initiation of second dose are performed with the same delivery device, *e.g.,* with the same cannula or reservoir.

In some examples, said second dose is administered for a period of time that is between 48 and 192 hours, 60 and 144 hours, 60 and 120 hours, 80 and 110 hours, and 90 and 100 hours. In some examples, said second dose is administered for 95+/-5 hours. In some examples, said second dose is administered for 95 hours.

In some examples, said second dose results in a plasma concentration of 50 to 500 nM, 100 to 400 nM, or 200 to 300 nM. In some examples, said second dose results in a plasma concentration of 500 to 1000 nM, 600 to 900 nM, or 700 to 800 nM. In some examples, said second dose results in a plasma concentration of 1000 to 1500 nM, 1100 to 1400 nM, or 1200 to 1300 nM. In some examples, said second dose results in a plasma concentration of 1500 to 2000 nM, 1600 to 1900 nM, or 1700 to 1800 nM. In some examples, said second dose results in a plasma concentration of 2000 to 2500 nM, 2100 to 2400 nM, or 2200 to 2300 nM. In some examples, said second dose results in a plasma concentration of 300 to 800 nM, 400 to 700 nM, or 500 to 600 nM. In some examples, said second dose results in a plasma concentration of 800 to 1300 nM, 900 to 1200 nM, or 1000 to 1100 nM. In some examples, said first dose results in a plasma concentration of 1300 to 1800 nM, 1400 to 1700 nM, or 1500 to 1600 nM. In some examples, said second dose results in a plasma concentration of 1800 to 2300 nM, 1900 to 2200 nM, or 2000 to 2100 nM. In some examples, said second dose results in a plasma concentration of 2300 to 2600 nM, 2400 to 2500 nM. In some examples, said second dose results in a plasma concentration of 300 to 400 nM, 400 to 500 nM, 600 to 700 nM, 800 to 900 nM, 1100 to 1200 nM, 1300 to 1400 nM, 1400 to 1500 nM, 1600 to 1700 nM, 1800 to 1900 nM, 1900 to 2000 nM, 2100 to 2200 nM, 2300 to 2400 nM. In some examples, said second dose results in a plasma concentration of 500 to 2500 nM, 500 to 1500 nM, 500 to 1000 nM, 500 to 800 nM, or 500 to 600 nM. In some examples, said second dose results in a plasma concentration of 50 to 250 nM, 100 to 200 nM, or 140 to 160 nM. In some examples, said second dose results in a plasma concentration of 150 +/- 30 nM, 150 +/- 20 nM, 150 +/- 10 nM, or 150 nM

In some examples, the plasma concentration of said second dose is measured at a preselected time, *e.g.,* at 10, 15, 20, 30, 45, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said second dose.

In some examples, said second dose results in a plasma concentration of 150 nM, *e.g.,* as measured at a preselected time, *e.g.,* at 10, 15, 20, 30, 45, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said second dose.

In some examples, said second dose is administered at the same infusion rate, e.g. amount of allopregnanolone /unit time, over the entire second dose. In some examples, the infusion rate, e.g. amount of allopregnanolone delivered/unit time varies during the second dose. In some examples, said second dose is administered at an infusion rate, e.g. amount of allopregnanolone/unit time of 25-1500 □g/kg/hour. In some examples, said second dose is administered at an infusion rate, e.g. amount of allopregnanolone/unit time of 25-150 □g/kg/hour, 50-100 □g/kg/hour, 75-100 □g/kg/hour, 85 □g/kg/hour, 86 □g/kg/hour, or 87 □g/kg/hour.

In some examples, said downward taper dose comprises administering a continuously decreasing amount allopregnanolone. In some examples, said downward taper dose comprises administering a continuously decreasing amount of allopregnanolone/unit time. In some examples, said downward taper dose comprises administering a plurality of step doses, wherein each subsequent step dose is lower than the step dose that precedes it. In some examples, said downward taper dose comprises administering a plurality of step doses, wherein each subsequent step dose delivers a lower amount of allopregnanolone/unit time than the step dose that precedes it.

In some examples, the method comprises administering a first, second, and third step dose. In some examples, said first step dose is 60 to 90% of the second/maintenance dose; said second step dose is 40 to 70% of the second/maintenance dose; and said third step dose is 10 to 40% of the second/maintenance dose. In some examples, the amount of allopregnanolone delivered/unit time in said first step dose is 60 to 90% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 70% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 10 to 40% of the infusion rate, e.g. amount of allopregnanolone delivered/unit time in said second/maintenance dose. In some examples, said first step dose is 70 to 80% of the second/maintenance dose; said second step dose is 40 to 60% of the second/maintenance dose; and said third step dose is 20 to 30%

of the second/maintenance dose. In some examples, the amount of allopregnanolone delivered/unit time in said first step dose is 70 to 80% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 60% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 20 to 30% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose. In some examples, said first step dose is 75% of the second/maintenance dose; said second step dose is 50% of the second/maintenance dose; and said third step dose is 25% of the second/maintenance dose. In some examples, the amount of allopregnanolone delivered/unit time in said first step dose is 75% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose. In some examples, the amount of allopregnanolone delivered/unit time in said second step dose is 50% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose. In some examples, the amount of allopregnanolone delivered/unit time in said third step dose is 25% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some examples, after the completion of said third step dose, no allopregnanolone is administered to the subject (*e.g.,* human subject) for at least 10, 20, 30, 40, 50, or 60 days, or until the patient has a subsequent episode of SRSE.

In some examples, said first step dose is administered at an amount of allopregnanolone/unit time of 25-1000 □g/kg/hour. In some examples, said first step dose is administered at an amount of allopregnanolone/unit time of 25-100 □g/kg/hour, 50-75 □g/kg/hour, 60-70 □g/kg/hour, 63 □g/kg/hour, 64 □g/kg/hour, or 65 □g/kg/hour. In some examples, said second step dose is administered at an amount of allopregnanolone/unit time of 10-700 □g/kg/hour□□□In some examples, said second step dose is administered at an amount of allopregnanolone/unit time of 10-70 □g/kg/hour, 25-55 □g/kg/hour, 40-50 □g/kg/hour, 42 □g/kg/hour, 43 □g/kg/hour, or 44 □g/kg/hour. In some examples, said third step dose is administered at an amount of allopregnanolone/unit time of 5-500 □g/kg/hour. In some examples, said third step dose is administered at an amount of allopregnanolone/unit time of 5-50 □g/kg/hour, 10-35 □g/kg/hour, 15-25 □g/kg/hour, 20 □g/kg/hour, 21 □g/kg/hour, or 22 □g/kg/hour.

In some examples, the third/taper dose begins no longer than 90, 80, 70, 60, or 30 minutes after the administration or end of the second dose. In some examples, the third/taper dose begins at the end of administration of the second dose.

In some examples, the administration of the second dose and the initiation of third/taper dose are performed with the same delivery device, *e.g.,* the same cannula.

In some examples, the time between the end of the administration of said first step dose and the initiation of administration of said second step dose is less than 120, 60, 30, 15 or 5 minutes.

In some examples, the time between the end of the administration of said second step dose and the initiation of administration of said third step dose is less than 120, 60, 30, 15 or 5 minutes.

In some examples, said third dose is administered for a period of time that is between 10 and 100 hours, 12 and 96 hours, 12 and 48 hours, 16 and 32 hours, or 20 and 30 hours.

In some examples, said third dose is administered over 24 hours.

In some examples, the allopregnanolone is provided in a composition comprising a cyclodextrin, *e.g.,* □-cyclodextrin, *e.g.,* sulfo butyl ether □-cyclodextrin, *e.g.,* CAPTISOL. In some examples, the allopregnanolone is provided at a concentration of 0.1 to 10 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone.

In some examples, the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition. In some examples, the cyclodextrin is present in the composition at 1, 2.5, 5, 10, 12, 13, 15, 30% by weight of cyclodextrin per volume of composition. In some examples, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition.

In some examples, the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL allopregnanolone. In some examples, the cyclodextrin is present in the composition at 1, 2.5, 5, 10, 12, 13, 15, 30% by

weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL allopregnanolone.

In some examples, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some examples, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some examples, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone. In some examples, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In some examples, the method further comprises, evaluating the subject (*e.g.,* human subject), wherein the evaluating comprises performing c-ECG. In some examples, the method comprises, evaluating the subject (*e.g.,* human subject), wherein the evaluating comprises performing EEG. In some examples, the method further comprises evaluating the subject (*e.g.,* human subject) for serum chemistry (*e.g.,* one or more of albumin, AST, ALT, bicarbonate, bilirubin, BUN, calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, or glucose). In some examples, the method further comprises, evaluating the subject (*e.g.,* human subject) for CBC (*e.g.,* one or more of RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, WBC with differential including neutrophils, eosinophils, basophils, lymphocytes, or monocytes. In some examples, the method further comprises evaluating the subject (*e.g.,* human subject) for serum allopregnanolone, progesterone, and 5□-dihydrotestosterone. In some examples, the method comprises comparing an observed value with a reference value.

In some examples, said subject (*e.g.,* human subject) is evaluated for a parameter described herein during said weaning period.

In one example, the present disclosure features a method of treating a subject (*e.g.,* human subject) having, SE, RSE, or SRSE comprising: administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 30-90 minutes; and results in a plasma level of allopregnanolone of 100-

2000 nM allopregnanolone; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 1-60 minutes after the end of the second dose; lasts for 1-6 days; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-100 hours; and results in a plasma level of allopregnanolone of 0-1500 nM allopregnanolone; wherein, collectively, the administrations are provided in sufficient amount to treat said subject (*e.g.,* human subject).

In some examples, the method comprises administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 70 to 110 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours.

In some examples, administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 70 to 110 hours; and administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24 +/- 2 hours and said third downward taper dose comprises a first, second, and third step dose.

In some examples, administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 85 to 105 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours and: the amount of allopregnanolone delivered/unit time in said first step dose is 70 to 80% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 60% of the amount of allopregnanolone delivered/unit time in

said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 20 to 30% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some examples, administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-5 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 96+/-4 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24+/-2 hours and: the amount of allopregnanolone delivered/unit time in said first step dose is 75% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 50% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 25% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some examples, the method further comprises administering an amount of a composition selected from benzodiazepines (*e.g.,* midazolam), propofol, barbiturates, and ketamine sufficient to place said subject (*e.g.,* human subject) under general anesthesia;

In one example, the present disclosure features a kit comprising one or more of: a preparation of allopregnanolone, *e.g.,* a plurality of preparations of allopregnanolone at a concentrations suitable for use at the first, second, and third doses; and instructions for use for treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* super-refractory status epilepticus (SRSE).

In some examples, the kit further comprises a suitable diluent (*e.g.,* water, saline, cyclodextrin, *e.g.,* □-cyclodextrin, *e.g.,* sulfo butyl ether □-cyclodextrin, *e.g.,* CAPTISOL).

In some examples, the allopregnanolone is provided at a concentration of 0.1-10 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 0.5-7.5 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 1-6 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some examples, the allopregnanolone is

provided at a concentration of 2.5 allopregnanolone. In some examples, the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In one example, the present disclosure features a method of making a series of dosages, the method comprising combining a diluent and allopregnanolone in proportions to form dosage forms suitable for use as the first, second and one or more step doses for said third dose.

In one example, the present disclosure features a method of adjusting the amount of diluents and / or allopregnanolone flowing into or out of a delivery device, *e.g.,* a catheter, reservoir, the method comprising altering, *e.g.,* decreasing, the flow rate of allopregnanolone flowing into the delivery device, so as to release in succession, two or more of a first dosage, a second dosage and one or more step doses of the third dose.

In one example, the present disclosure features a method of treating a subject having seizure, epilepsy or status epilepticus by administering in combination to the subject a neuroactive steroid and a benzodiazepine or anesthetic/sedative. In some examples, the method further comprises administering at least one of the neuroactive steroid and benzodiazepine or anesthetic/sedative parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some examples, both the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered parenterally.

In some examples, the neuroactive steroid and benzodiazepine or anesthetic/sedative co-administered (*e.g.,* administered simultaneously, administered concurrently). In some examples, the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered sequentially. In some examples, neuroactive steroid and benzodiazepine or anesthetic/sedative are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine or anesthetic/sedative) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in the absence of the combination regimen. The agents may be administered separately, as part of a multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this disclosure in a single composition.

In some examples, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone. In an example, the neuroactive steroid is allopregnanolone.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, is formulated for parenteral administration (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, is administered in a composition comprising a cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex.

In some examples, the cyclodextrin is a β-cyclodextrin. In an example, the cyclodextrin is a sulfo butyl ether β-cyclodextrin. In an example, the cyclodextrin is CAPTISOL®. In some examples, the cyclodextrin is a β-cyclodextrin disclosed in U.S. Patent Nos. 5,874,418; 6,046,177; or 7,635,733, which are herein incorporated by reference.

In some examples, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone, and the cyclodextrin is a β-cyclodextrin. In some examples, the neuroactive steroid is a progestin derivative, *e.g.,* allopregnanolone, and the cyclodextrin is a sulfo butyl ether β-cyclodextrin. In an example, the neuroactive steroid is allopregnanolone and the cyclodextrin is CAPTISOL®.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated for parenteral administration. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration between 0.25-30mg/mL, 0.5-30mg/mL; 1-30mg/mL; 5-30mg/mL, 10-30mg/mL; 15-30mg/mL, 0.25-20mg/mL; 0.5-20mg/mL; 1-20mg/mL, 0.5-20mg/mL; 1-20mg/mL, 5-20mg/mL, 10-20mg/mL, 0.25-15mg/mL, 0.5-15mg/mL; 0.5-10mg/mL; 0.5-7 mg/mL; 1-15mg/mL, 1-10mg/mL; 1-7 mg/mL; 1-5mg/mL; 5-15mg/mL; 5-10mg/mL; 10-15mg/mL; 1-10mg/mL; 2-8mg/mL; 2-7mg/mL; 3-5mg/mL; 5-15mg/mL; 3-7 mg/mL; 4-6 mg/mL; 7-12mg/mL; 7-10mg/mL; 8-9mg/mL; 3-5mg/mL; or 3-4mg/mL. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive

steroid at a concentration of 0.25mg/mL, 0.5mg/mL; 1.0mg/mL; 1.5mg/mL; 2.0mg/mL; 2.5mg/mL; 3.0mg/mL; 3.5mg/mL; 4.0mg/mL; 4.5mg/mL; 5.0mg/mL, 5.5mg/mL, 6.0mg/mL, 6.5mg/mL, 7.0mg/mL, 7.5mg/mL, 8.0mg/mL, 8.5mg/mL, 9.0mg/mL, 9.5mg/mL, 10mg/mL, 15mg/mL, 20mg/mL, 25mg/mL, or 30 mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 1.5mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 2.5mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 3.5mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 5 mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 6 mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 15 mg/mL.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of between 0.1-50 □M; 0.1-40 □M; 0.1-30 □M; 0.1-20 □M; 0.1-15 □M; 0.5-50 □M; 0.5-40 □M; 0.5-30 □M; 0.5-20 □M; 0.5-15 □M; 1-50 □M; 1-40 □M; 1-30 □M; 1-20 □M; 1-15 □M; 2-50 □M; 2-40 □M; 2-30 □M; 2-20 □M; 2-15 □M; 0.5-15 □M; 1-15 □M; 2-15 □M; 3-15 □M; 1-20 □M. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 0.1 □M; 0.5-1 □M; 2 □M; 4

□M; 5 □M; 7 □M; 10 □M; 15 □M; 20 □M; 25 □M; 40□M; 50 □M. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 1 □M. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 2 □M. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration of 5 □M.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration between 25-400mg/mL; 25-300mg/mL; 25-200mg/mL; 25-100mg/mL; 25-50mg/mL; 50-400mg/mL; 50-300mg/mL; 60-400mg/mL; 60-300mg/mL; 150-400mg/mL; 150-300mg/mL; 200-300mg/mL; 200-400mg/mL; 30-100mg/mL; 30-300mg/mL; 30-400mg/mL; 45-75mg/mL; 50-70mg/mL; 55-65mg/mL; or 50-60mg/mL. In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 25mg/mL; 30mg/mL; 35mg/mL; 40mg/mL; 45mg/mL; 50mg/mL; 55mg/mL; 60mg/mL; 65mg/mL; 70mg/mL; 75mg/mL; 80mg/mL; 85mg/mL; 90mg/mL, 95mg/mL; 100mg/mL; 150mg/mL; 200mg/mL; 250mg/mL; 300mg/mL; 350mg/mL; or 400mg/mL. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 60mg/mL.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising between 2.5-40%, 2.5-30%, 2.5-20%, 2.5-15%, 2.5-10%, 5-40%, 5-30%, 5-20%, 5-15%, 5-10%, 6-40%, 6-30%, 6-20%, 6-10%, 6-20%, 6-30%, 10-40%, 10-

30%, 10-20%, 20-40%, 20-30%, 25-40%, 25-30%, 3-10%, 3-15%, 4.5-7.5%, 4-13%, 5-7%, 5-13%, 5.5-6.5%, 7-13% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In some examples, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 2.5%, 3%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, 10%, 12%, 15%, 20%, 25%, 30%, 35% or 40% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 6% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 15% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising 30% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 1.5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 6% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 6% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin,

e.g., CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 6% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 1.25mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 1.5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 2.5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 3.75mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin,

e.g., a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 12% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 1.5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 15% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 15% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 15% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 1.5mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 30% by weight of the cyclodextrin, *e.g.,*

CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 30% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution. In an example, the neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid, *e.g.,* allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, at a concentration of 30% by weight of the cyclodextrin, *e.g.,* CAPTISOL® per weight of solution.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH between 3-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-9, 5-8, 5-7, 5-6, 4.5-7.5, or 5.5-7.5. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, or 9. In an example, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 6.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered intravenously. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered intramuscularly.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered between 1-10, 1-5, 5-10, 1-6, 2-6, 3-6, 4-5, or 1-9 consecutive days. In an example, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered for 5 consecutive days. In some examples, the duration of administration is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days. In some examples, the duration of administration is 3-7, 4-6, 4-5, or 5-6 days. In some examples, the duration of administration is 5 days.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at the same dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

consecutive days. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days. In an example, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose of 0.25mg/mL, 0.5mg/mL; 1.0mg/mL; 1.5mg/mL; 2.0mg/mL; 2.5mg/mL; 3.0mg/mL; 3.5mg/mL; 4.0mg/mL; 4.5mg/mL; 5.0mg/mL, 5.5mg/mL, 6.0mg/mL, 6.5mg/mL, 7.0mg/mL, 7.5mg/mL, 8.0mg/mL, 8.5mg/mL, 9.0mg/mL, 9.5mg/mL, 10mg/mL, 15mg/mL, 20mg/mL, 25mg/mL, or 30 mg/mL neuroactive steroid, *e.g.,* allopregnanolone, for 1 day and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, or 6 consecutive days of 0.25mg/mL, 0.5mg/mL; 1.0mg/mL; 1.5mg/mL; 2.0mg/mL; 2.5mg/mL; 3.0mg/mL; 3.5mg/mL; 4.0mg/mL; 4.5mg/mL; 5.0mg/mL, 5.5mg/mL, 6.0mg/mL, 6.5mg/mL, 7.0mg/mL, 7.5mg/mL, 8.0mg/mL, 8.5mg/mL, 9.0mg/mL, 9.5mg/mL, 10mg/mL, 15mg/mL, 20mg/mL, 25mg/mL, or 30 mg/mL neuroactive steroid, *e.g.,* allopregnanolone. In some examples, a maintenance, *e.g.,* infusion, dose described herein, is lower than a load, *e.g.,* bolus, dose described herein. In some examples, a maintenance, *e.g.,* infusion, dose described herein, is the same as a load, *e.g.,* bolus, dose described herein. In some examples, the maintenance, *e.g.,* infusion, dose is less than 0.25mg/mL, 0.5mg/mL; 1.0mg/mL; 1.5mg/mL; 2.0mg/mL; 2.5mg/mL; 3.0mg/mL; 3.5mg/mL; 4.0mg/mL; 4.5mg/mL; 5.0mg/mL, 5.5mg/mL, 6.0mg/mL, 6.5mg/mL, 7.0mg/mL, 7.5mg/mL, 8.0mg/mL, 8.5mg/mL, 9.0mg/mL, 9.5mg/mL, 10mg/mL, 15mg/mL, 20mg/mL, 25mg/mL, or 30 mg/mL.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a taper dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a first step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours.

In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

consecutive days and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a first step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours and then administered at a second step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered at a load, *e.g.,* bolus, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a maintenance, *e.g.,* infusion, dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days and then administered at a first step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours and then administered at a second step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours and then administered at a third step dose for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours.

In some examples the first, second, or third step dose is less than the maintenance, *e.g.,* infusion, dose. In some examples, the second taper or third step dose is less than the first step dose. In some examples, the third step dose is less than the second step dose. In some examples, the first step dose is 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of the maintenance, *e.g.,* infusion, dose. In some examples, the first step dose is between 95-50%, 75-50%, 85-50%, 90-50%, 80-50%, or 75-100% of the maintenance, *e.g.,* infusion, dose. In an example, the first step dose is 75% of the maintenance, *e.g.,* infusion, dose.

In some examples, the second step dose is 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of the maintenance, *e.g.,* infusion, dose. In some examples, the second step dose is between 95-30%, 75-30%, 85-30%, 60-30%, 70-30%, 50-30%, or 50-40% of the maintenance, *e.g.,* infusion, dose. In an example, the second step dose is 50% of the maintenance, *e.g.,* infusion, dose.

In some examples, the third step dose is 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% of the maintenance, *e.g.,* infusion, dose. In some examples, the third step dose is between 50-5%, 40-5%, 30-5%, 25-5%, 25-10%, 25-20%, or 25-40% of the maintenance, *e.g.,* infusion, dose. In an example, the second step dose is 50% of the maintenance, *e.g.,* infusion, dose. In an example, the third step dose is 25% of the maintenance, *e.g.,* infusion, dose.

In an example, a composition comprising a neuroactive steroid, *e.g.,* allopregnanolone, and cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, complex, comprises less than 100ppm of a phosphate, and the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U.

due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 300 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to a color forming agent, as determined by UV/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 20 ppm of a sulfoalkylating agent; less than 0.5% wt. of an underivatized cyclodextrin; less than 1% wt. of an alkali metal halide salt; and less than 0.25% wt. of a hydrolyzed sulfoalkylating agent.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 50 ppm of a phosphate; less than 10 ppm of a sulfoalkylating agent; less than 0.2% wt. of an underivatized cyclodextrin; less than 0.5% wt. of an alkali metal halide salt; and less than 0.1% wt. of a hydrolyzed sulfoalkylating agent; and wherein the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.2 A.U. due to the color-forming agent, as determined by U/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 10 ppm of a phosphate; less than 2 ppm of a sulfoalkylating agent; less than 0.1% wt. of an underivatized cyclodextrin; less than 0.2% wt. of an alkali metal halide salt; and less than 0.08% wt. of a hydrolyzed sulfoalkylating agent; and

wherein the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, has an absorption of less than 0.1 A.U. due to the color-forming agent, as determined by UV/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, per mL of solution in a cell having a 1 cm path length.

In some examples, the cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®, further comprises: less than 5 ppm of a phosphate; less than 0.1% wt. of an alkali metal halide salt; and less than 0.05% wt. of a hydrolyzed sulfoalkylating agent.

In some examples, the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered within 48 hours, 24 hours, 10 hours, 8 hours, 5 hours, 3 hours, 1 hour, or 0.5 hour after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has started. In some examples, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered within 60 minutes, 45 minutes, 30 minutes, 15 minutes, 10 minutes, or 5 minutes after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has started. In some examples, the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered after a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure has lasted 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes or 60 minutes.

In some examples, the neuroactive steroid (*e.g.,* allopregnanolone) and CAPTISOL® complex is formulated as an aqueous composition and is administered prior to the onset of a seizure, *e.g.,* a status epileptic seizure, *e.g.,* a refractory status epileptic seizure.

In some examples, the benzodiazepine is clonazepam, lorazepam, midazolam, or diazepam.

In some examples, the benzodiazepine is formulated for oral delivery. In some examples, the benzodiazepine is formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, the anesthetic/sedative is propofol or a barbiturate, *e.g.,* pentobarbital.

In some examples, both the neuroactive steroid and the benzodiazepine or anesthetic/sedative are formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some examples, the neuroactive steroid such as allopregnanolone and benzodiazepine or anesthetic/sedative, when administered in combination, are administered in an amount sufficient to achieve burst suppression (*e.g.,* a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM). In some examples, the neuroactive steroid such as allopregnanolone and benzodiazepine or anesthetic/sedative, when administered in combination, is administered at a dose sufficient to achieve a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds, 5-30 seconds, 10-30 seconds, 15-30 seconds, 1-30 seconds, 0-30 seconds, 2-20 seconds, 2-10 seconds, 5-20 seconds, 10-20 seconds, 15-25 seconds, 5-15 seconds or 5-10 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM.

Brief Description of the Figures

FIG 1. Physical appearance of ALLO formulations with Captisol.

FIG 2. Plasma exposure of allopregnanolone from human SE study. Plasma concentration profile over time of allopregnanolone in a single male patient. The patient was dosed allopregnanolone (ALLO) at 1.5 mg/mL in 6% hydroxypropyl-β-cyclodextrin in 0.9% sodium chloride intravenously for 5 days (120 h). The infusion rate was 86 μg/kg/h. The patient was dosed 5.6 mg/h of allopregnanolone at 3.8 mL/h. Plasma concentration was analyzed 2 hours prior to the start of infusion and then 52, 76, 100, 124, and 148 hours post-infusion.

Detailed Description of the Invention

As used herein, "administered in combination" or a combined administration of two agents (*e.g.,* a neuroactive steroid and a benzodiazepine or anesthetic/sedative) means that two or more

Claims:

1. A method of preparing a formulation comprising allopregnanolone, said method comprising the step of high shear mixing an aqueous solution comprising 5 mg/mL allopregnanolone and 25% sulfo butyl ether beta-cyclodextrin for a time period of one hour.

2. The method of claim 1, wherein the step of high shear mixing for a time period of one hour is characterized by a clear aqueous solution comprising 5 mg/mL allopregnanolone and 25% sulfo butyl ether beta-cyclodextrin.