NEUROACTIVE STEROID FORMULATIONS AND METHODS OF TREATING CNS DISORDERS

Field of the Invention

The present invention generally relates to neuroactive steroid formulations, particularly allopregnanolone, for the treatment of CNS injuries and/or diseases.

Cross-Reference to Related Applications

This application claims priority from U.S.S.N. 61/589,740 filed January 23, 2012, the teachings of which are incorporated herein.

Background of the Invention

Central nervous system (CNS) related disorders include disorders which affect either or both the brain or spinal cord. CNS related disorders can include, e.g., a traumatic injury, e.g., a traumatic brain injury. A traumatic injury to the CNS is characterized by a physical impact to the central nervous system, e.g., a traumatic brain injury. Status epilepticus (SE) is another example of a CNS related disorder, e.g., generalized status epilepticus, early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus, non-convulsive status epilepticus, e.g., complex partial status epilepticus.

Summary

The disclosure features, *inter alia*, compositions comprising a neuroactive steroid, e.g., allopregnanolone, and optionally 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®. The disclosure also features, *inter alia*, methods of treating a subject having a CNS disorder, e.g., a traumatic brain injury, status epilepticus, e.g., refractory convulsive status

epilepticus, non-convulsive status epilepticus, the methods comprising administering to the subject a composition described herein, e.g., a neuroactive steroid, e.g., allopregnanolone, and optionally 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®..

Provided herein is use of an effective amount of a dosage formulation of allopregnanolone in a cyclodextrin carrier in the manufacture of a medicament for treating a traumatic brain injury in an individual in need thereof for treatment of a central nervous system injury.

In one aspect, there is provided an aqueous pharmaceutical composition formulated for parental administration comprising allopregnanolone at a concentration between 1-10 mg/mL and sulfo butyl ether-β cyclodextrin at a concentration between 25-400 mg/mL.

In one aspect, there is provided use of the aqueous pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a CNS disorder.

Provided herein is use of an effective amount of a dosage formulation of allopregnanolone in the manufacture of a medicament for treating a CNS disorder in a subject, wherein the CNS disorder is a seizure or status epilepticus.

In one embodiment, the disclosure features a composition, the composition comprising a neuroactive steroid, e.g., allopregnanolone, and cyclodextrin, e.g., a neuroactive steroid, e.g., allopregnanolone, and optionally 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®, complex.

In some embodiments, the neuroactive steroid is a progestin derivative, e.g., allopregnanolone. In an embodiment, the neuroactive steroid is allopregnanolone.

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

In some embodiments, 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 embodiment, the neuroactive steroid, e.g., allopregnanolone, and cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g.,

We claim:

1. An aqueous pharmaceutical composition formulated for parental administration comprising allopregnanolone at a concentration between 1-10 mg/mL and sulfo butyl ether-β-cyclodextrin at a concentration between 25-400 mg/mL.

2. An aqueous pharmaceutical composition as claimed in claim 1, comprising allopregnanolone at a concentration between 1-5 mg/mL.

3. An aqueous pharmaceutical composition as claimed in claim 1, comprising allopregnanolone at a concentration between 5-10 mg/mL.

4. An aqueous pharmaceutical composition as claimed in claim 1, comprising allopregnanolone at a concentration between 3-5 mg/mL.

5. An aqueous pharmaceutical composition as claimed in claim 1, comprising allopregnanolone at a concentration of 5 mg/mL.

6. An aqueous pharmaceutical composition as claimed in claim 5, comprising sulfo butyl ether-β--cyclodextrin at a concentration between 200-400mg/mL.

7. An aqueous pharmaceutical composition as claimed in claim 5, comprising sulfo butyl ether-β-cyclodextrin at a concentration of 250mg/mL.

8. An aqueous pharmaceutical composition as claimed in any one of claims 1 to 7, wherein the pH of the composition is between 5 to 9.

9. An aqueous pharmaceutical composition as claimed in any one of claims 1 to 8, wherein the pH of the composition is 6.

10. An aqueous pharmaceutical composition as claimed in any one of claims 1 to 9, wherein the formulation comprises an antioxidant.

11. An aqueous pharmaceutical composition as claimed in any one of claims 1 to 10, wherein the formulation comprises a buffer.

12. An aqueous pharmaceutical composition as claimed in claim 11, wherein the buffer is selected from a phosphate buffer, acetate buffer, or citrate buffer.

13. An aqueous pharmaceutical composition as claimed in any one of claims 1 to 12, wherein the composition is formulated for intravenous administration.

14. Use of the aqueous pharmaceutical composition as claimed in any one of claims 1 to 13 in the manufacture of a medicament for treating a CNS disorder.

15. The use of claim 14, wherein the CNS disorder is a traumatic brain injury, a seizure or status epilepticus.

16. The use of claim 15, wherein the status epilepticus disorder is refractory status epilepticus or non-convulsive status epilepticus and wherein the seizure is an acute repetitive seizure or a cluster seizure.