SUMMARY

In accordance with the instant disclosure, methods for inhibiting, treating, and/or preventing a disorder associated with a deficiency in C1 esterase inhibitor in a subject are provided. In a particular embodiment, the method comprises administering a composition comprising at least one C1 esterase inhibitor.

In accordance with the instant disclosure, therapeutic compositions are also provided. In a particular embodiment, the composition comprises at least one C1 esterase inhibitor and, optionally, at least one pharmaceutically acceptable carrier for delivery (e.g. intravenous or subcutaneous delivery). Kits comprising a composition comprising at least one C1 esterase inhibitor are also provided herein.

In one aspect of the present disclosure, there is provided a composition comprising at least one C1 esterase inhibitor wherein the at least one C1 esterase inhibitor is present at 400U/ml or more for use in treating, inhibiting, or preventing hereditary angioedema (HAE) and wherein said composition is to be administered subcutaneously.

In another aspect of the present disclosure, there is provided a use of at least one C1 esterase inhibitor, in the manufacture of a medicament for treating, inhibiting, or preventing hereditary angioedema (HAE), wherein the at least one C1 esterase inhibitor is present at 400U/ml or more, and wherein said medicament is to be administered subcutaneously.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides an amino acid sequence of human C1 esterase inhibitor.

Figure 2 provides a graph of the effect of protein concentration on viscosity for initial spin concentration samples.

DETAILED DESCRIPTION OF THE INVENTION

The restoration of active C1 esterase inhibitor levels in patients having a disorder associated with deficient or reduced levels of active C1 esterase inhibitor (e.g., HAE) is an effective measure for treating such disorders. Currently, C1 esterase inhibitor (such as Cinryze® (ViroPharma, Inc.; Exton, PA)) is administered to a patient intravenously by a medical professional. Herein, formulations of a C1 esterase inhibitor (such as Cinryze®) are provided which are also effective for subcutaneous (SC) administration. Surprisingly, the subcutaneous administration of the C1 esterase inhibitor is sufficient to maintain the blood levels of the C1 esterase inhibitor. The SC administration of a C1 esterase inhibitor fulfills an unmet medical need due to the limitations of intravenous administration in HAE patients.

In accordance with the instant invention, compositions and methods for inhibiting (e.g., reducing or slowing), treating, and/or preventing a disorder associated with C1 esterase inhibitor deficiency in a subject are provided. In a particular embodiment, the methods comprise administering (e.g., subcutaneously or intravenously) to a subject in need thereof at least one C1 esterase inhibitor. In a particular embodiment, the C1 esterase inhibitor is administered subcutaneously after an initial administration of the C1 esterase inhibitor intravenously.

Claims

1. A composition comprising at least one C1 esterase inhibitor wherein the at least one C1 esterase inhibitor is present at 400U/ml or more for use in treating, inhibiting, or preventing hereditary angioedema (HAE) and wherein said composition is to be administered subcutaneously.

2. The composition for use according to claim 1, wherein the at least one C1 esterase inhibitor is present at up to 500 U/ml.

3. The composition for use according to claim 1 or claim 2, wherein the at least one C1 esterase inhibitor is to be administered at a dose ranging from 500 Units to about 5,000 Units, 1,000 Units to 3,500 Units, or 1,500 Units to 2,500 Units.

4. The composition for use according to any one of the preceding claims, wherein the at least one C1 esterase inhibitor is to be administered daily, every other day, every 3 days, once a week, twice a week or three times a week.

5. The composition for use according to any one of the preceding claims, wherein the subject is to be administered a high initial dose of the at least one C1 esterase inhibitor, followed by lower maintenance doses,
optionally wherein the high initial dose is at least 1.5, 2, 3, 4, or 5 times the subsequent doses, and/or the high initial dose is to be administered intravenously and the at least one C1 esterase inhibitor is to be subsequently administered subcutaneously.

6. The composition for use according to any preceding claim, wherein the administration of the at least one C1 esterase inhibitor leads to increased levels of the C1 esterase inhibitor in the blood of the subject, wherein the blood levels of the C1 esterase inhibitor are increased to at least 0.3 U/mL, 0.4 U/mL, or up to 1 U/mL.

7. The composition for use according to any preceding claim, wherein the blood levels of the C1 esterase inhibitor are maintained at or above 0.4 U/mL for at least 50%, at least 75%, at least 90%, or at least 95% of the time.

8. The composition for use according to any preceding claim, wherein:

(i) the hereditary angioedema is Type I or Type II HAE,
(ii) the administration of the at least one C1 esterase inhibitor results in HAE prophylactic treatment,
(iii) the treatment of HAE results in at least a reduction in the severity and/or number of HAE attacks, or

(iv) the administration of the at least one C1 esterase inhibitor results in treatment of an HAE attack.

9. The composition for use according to any preceding claim, wherein the at least one C1 esterase inhibitor is isolated or purified from human plasma or is recombinantly produced, and/or
wherein the C1 esterase inhibitor has an amino acid sequence at least 90%, 95%, 98%, 99% or 100% identical to the human C1 esterase inhibitor amino acid sequence of Figure 1.

10. The composition for use according to any preceding claim, wherein the composition comprises a buffer which comprises citrate or sodium citrate, optionally 5mM to 50 mM sodium citrate, 10 mM to 30 mM sodium citrate, or 20 mM sodium citrate.

11. The composition for use according to any one of claims 1-9, comprising a buffer wherein the buffer does not contain citrate or citric acid.

12. The composition for use according to any preceding claim, wherein the composition:

(i) comprises at least one amino acid or salt thereof; and/or
(ii) has a pH of between 6.5 and 8.0.

13. The composition for use according to any preceding claim wherein the composition is formed from a lyophilized form by reconstitution in a buffer prior to administration.

14. Use of at least one C1 esterase inhibitor, in the manufacture of a medicament for treating, inhibiting, or preventing hereditary angioedema (HAE), wherein the at least one C1 esterase inhibitor is present at 400U/ml or more, and wherein said medicament is to be administered subcutaneously.

15. The use according to claim 14, wherein the at least one C1 esterase inhibitor is present at up to 500 U/ml.

16. The use according to claim 14 or claim 15, wherein the at least one C1 esterase inhibitor is to be administered at a dose ranging from 500 Units to about 5,000 Units, 1,000 Units to 3,500 Units, or 1,500 Units to 2,500 Units.

17. The use according to any one of claims 14 to 16, wherein the at least one C1 esterase inhibitor is to be administered daily, every other day, every 3 days, once a week, twice a week or three times a week.

18. The use according to any one of claims 14 to 17, wherein the subject is to be administered a high initial dose of the at least one C1 esterase inhibitor, followed by lower maintenance doses,
optionally wherein the high initial dose is at least 1.5, 2, 3, 4, or 5 times the subsequent doses, and/or the high initial dose is to be administered intravenously and the at least one C1 esterase inhibitor is to be subsequently administered subcutaneously.

19. The use according to any one of claims 14 to 18, wherein the administration of the at least one C1 esterase inhibitor leads to increased levels of the C1 esterase inhibitor in the blood of the subject, wherein the blood levels of the C1 esterase inhibitor are increased to at least 0.3 U/mL, 0.4 U/mL, or up to 1 U/mL.

20. The use according to any one of claims 14 to 19, wherein the blood levels of the C1 esterase inhibitor are maintained at or above 0.4 U/mL for at least 50%, at least 75%, at least 90%, or at least 95% of the time.

21. The use according to any one of claims 14 to 20, wherein:

(i) the hereditary angioedema is Type I or Type II HAE,
(ii) the administration of the at least one C1 esterase inhibitor results in HAE prophylactic treatment,
(iii) the treatment of HAE results in at least a reduction in the severity and/or number of HAE attacks, or
(iv) the administration of the at least one C1 esterase inhibitor results in treatment of an HAE attack.

22. The use according to any one of claims 14 to 21, wherein the at least one C1 esterase inhibitor is isolated or purified from human plasma or is recombinantly produced, and/or wherein the C1 esterase inhibitor has an amino acid sequence at least 90%, 95%, 98%, 99% or 100% identical to the human C1 esterase inhibitor amino acid sequence of Figure 1.

23. The use according to any one of claims 14 to 22, wherein the medicament comprises a buffer which comprises citrate or sodium citrate, optionally 5mM to 50 mM sodium citrate, 10 mM to 30 mM sodium citrate, or 20 mM sodium citrate.

24. The use according to any one of claims 14 to 22, comprising a buffer wherein the buffer does not contain citrate or citric acid.

25. The use according to any one of claims 14 to 24, wherein the medicament:

(i) comprises at least one amino acid or salt thereof; and/or

(ii) has a pH of between 6.5 and 8.0.

26. The use according to any one of claims 14 to 25 wherein the medicament is formed from a lyophilized form by reconstitution in a buffer prior to administration.