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 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.

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 prophylactic treatment of hereditary angioedema (HAE), comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor has a concentration of about 400-600 U/mL, wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of Figure 1, wherein the medicament is to be administered, and wherein administration of the medicament increases the level of the C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, and wherein said medicament is to be administered subcutaneously.

In a further aspect of the present disclosure, there is provided a use of at least one C1 esterase inhibitor, in the manufacture of a medicament for treatment of hereditary angioedema (HAE), comprising a C1 esterase inhibitor, a buffer selected from citrate or phosphate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor is administered at a concentration of at least about 400 U/mL and a dose of at least about 1000 U, and wherein administration of the medicament comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the

subject to at least about 0.4 U/mL, and wherein the C1 esterase inhibitor comprises an amino acid sequence at least 95% identical to residues 23 to 500 of Figure 1, and wherein said medicament is to be administered subcutaneously.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor has a concentration of about 400 - 600 U/mL, and wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of Figure 1.

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. 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.

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

3. The 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 U to about 5,000 U, 1,000 Uto 3,500 U, or 1,500 U to 2,500 U.

4. The use according to any one of claims 1 to 3, 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 use according to any one of claims 1 to 4, 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 use according to any one of claims 1 to 5, 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 use according to any one of claims 1 to 6, 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 between administrations.

8. The use according to any one of claims 1 to 7, 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 use according to any one of claims 1 to 8, 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 use according to any one of claims 1 to 9, 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.

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

12. The use according to any one of claims 1 to 11, 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.

13. The use according to any one of claims 1 to 12 wherein the medicament 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 prophylactic treatment of hereditary angioedema (HAE), comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor has a concentration of about 400-600 U/mL, wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of Figure 1, wherein the medicament is to be administered, and wherein administration of the medicament increases the level of the C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, and wherein said medicament is to be administered subcutaneously.

15. The use of claim 1, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL.

16. The use of claim 14 or 15, wherein the medicament is reconstituted with water from at least one lyophilized powder comprising at least about 2000 U C1 esterase inhibitor and less than about 5000 U C1 esterase inhibitor.

17. The use of claim 14 or 15, wherein the C1 esterase inhibitor is to be administered in a range of about 1500 U to about 2500 U.

18. The use of claim 14 or 15, wherein at least about 2000 U of C1 esterase inhibitor is to be administered.

19. The use of claim 14 or 15, wherein the C1 esterase inhibitor is to be administered at a dose of about 5000 U.

20. The use of claim 14 or 15, wherein the C1 esterase inhibitor is to be administered in doses of at least about 2000 U and less than about 5000 U.

21. The use of claim 14 or 15, wherein the medicament is to be administered daily, every other day, or every three days.

22. The use of claim 14 or 15, wherein the medicament is to be administered one, two, or three times a week.

23. The use of claim 14 or 15, wherein the medicament is to be administered three or more times per week.

24. The use of claim 14 or 15, wherein administration of the medicament increases the level of functional C1 esterase inhibitor in the blood of the subject to or above 0.4 U/mL.

25. The use of claim 14 or 15, wherein administration of the medicament maintains the level of functional C1 esterase inhibitor in the blood of the subject at or above 0.4 U/mL for at least 50% of the time between administrations.

26. The use of claim 14 or 15, wherein administration of the medicament maintains the level of functional C1 esterase inhibitor in the blood of the subject at or above 0.4 U/mL for at least 75% of the time between administrations.

27. The use of claim 14 or 15, wherein administration of the medicament maintains the level of functional C1 esterase inhibitor in the blood of the subject at or above 0.4 U/mL for at least 90% of the time between administrations.

28. The use of claim 14 or 15, wherein administration of the medicament maintains the level of functional C1 esterase inhibitor in the blood of the subject at or above 0.4 U/mL for at least 95% of the time between administrations.

29. The use of claim 14 or 15, wherein the functional C1 esterase inhibitor blood levels are maintained above 0.4 U/mL for at least 95% of the time between administrations.

30. The use of claim 14 or 15, wherein the functional C1 esterase inhibitor blood levels are maintained above 0.4 U/mL for 100% of the time between administrations.

31. The use of claim 14 or 15, wherein administration of the medicament results in the treatment of HAE, wherein the treatment consists of subcutaneously administering said composition.

32. The use of claim 14 or 15, wherein administration of the medicament results in the prophylactic treatment, wherein the treatment consists of one or more subcutaneous administrations of said medicament .

33. The use of claim 14 or 15, wherein the use does not comprise an initial intravenously administered dose of C1 esterase inhibitor.

34. The use of claim 14 or 15, wherein administration of the medicament results in at least a reduction in the severity and/or number of HAE attacks.

35. The use of claim 14 or 15, wherein the medicament is reconstituted from a lyophilized powder prior to administration.

36. The use of claim 35, wherein the lyophilized powder is reconstituted with sterile water.

37. The use of claim 14 or 15, wherein the medicament is to be administered by the subject.

38. The use of claim 14 or 15, wherein the subject in need thereof is an adolescent human.

39. The use of claim 14 or 15, wherein the pH is between about 6.5 to about 7.5.

40. The use of claim 14 or 15, wherein the pH is between about 6.5 to about 7.0.

41. The use of claim 14 or 15, wherein the sodium citrate is present at about 10 mM to about 30mM.

42. The use of claim 14 or 15, wherein the sodium citrate is present at 10 mM to 30 mM.

43. The use of claim 14 or 15, wherein the sodium citrate is present at about 10 mM.

44. The use of claim 14 or 15, wherein the medicament is a monoformulation of active pharmaceutical ingredient consisting essentially of C1 esterase inhibitor.

45. Use of at least one C1 esterase inhibitor, in the manufacture of a medicament for treatment of hereditary angioedema (HAE), comprising a C1 esterase inhibitor, a buffer selected from citrate or phosphate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor is administered at a concentration of at least about 400 U/mL and a dose of at least about 1000 U, and wherein administration of the medicament comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, and wherein the C1 esterase inhibitor comprises an amino acid sequence at least 95% identical to residues 23 to 500 of Figure 1, and wherein said medicament is to be administered subcutaneously.

46. The use of claim 45, wherein the C1 esterase inhibitor is present in the medicament in a concentration of at least about 500 U/mL in the medicament .

47. The use of claim 45, wherein the medicament is to be administered daily, every other day, or every three days.

48. The use of claim 45, wherein the medicament is to be administered one, two, or three times a week.

49. The use of claim 45, wherein the increased blood levels of C1 esterase inhibitor are maintained at least 50% of the time between administrations.

50. The use of claim 45, wherein the HAE is Type I HAE or Type II HAE.

51. The use of claim 45, wherein the administration of the medicament comprising a C1 esterase inhibitor results in HAE prophylactic treatment.

52. The use of claim 45, wherein the administration of the medicament comprising a C1 esterase inhibitor results in treatment of an HAE attack.

53. The use of claim 45, wherein the administration of the medicament results in at least a reduction in the severity and/or number of HAE attacks.

54. The use of claim 45, wherein the C1 esterase inhibitor is purified from plasma.

55. The use of claim 45, wherein the C1 esterase inhibitor is recombinantly produced.

56. The use of claim 45, wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of Figure 1.

57. The use of claim 45, wherein the medicament is a liquid formulation.

58. The use of claim 45, wherein the medicament is reconstituted from lyophilized powder.

59. The use of claim 45, wherein the administration of the medicament comprising the C1 esterase inhibitor increases the level of C1 esterase inhibitor are maintained at least 50% of the time between administrations.

60. The use of claim 59, wherein the increased blood levels of C1 esterase inhibitor are maintained at least 50% of the time between administrations.

61. The use of claim 45, wherein the buffer is citrate.

62. The use of claim 45, wherein the buffer is phosphate.

63. A pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5-8.0, wherein the C1 esterase inhibitor has a concentration of about 400 - 600 U/mL, and wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of Figure 1.

64. The pharmaceutical composition of claim 63, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL.

65. The pharmaceutical composition of claim 63 or 64, wherein the pH is between about 6.5 to about 7.5.

66. The pharmaceutical composition of claim 63 or 64, wherein the pH is between about 6.5 to about 7.0.

67. The pharmaceutical composition of claim 63 or 64, wherein the sodium citrate is present at about 10 mM to about 30 mM.

68. The pharmaceutical composition of claim 63 or 64, wherein the sodium citrate is present at 10 mM to 30 mM.

69. The pharmaceutical composition of claim 63 or 64, wherein the sodium citrate is present at about 10 mM.

70. The pharmaceutical composition of claim 63 or 64, wherein the composition further comprises at least one amino acid or salt thereof.

71. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor is present in the composition in the range of about 1500 U to about 2500 U.

72. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor is present in the composition in at least about 2000 U.

73. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor is present in the composition at about 2000 U.

74. The pharmaceutical composition of claim 72, wherein the C1 esterase inhibitor is present in the composition less than about 5000 U.

75. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor is present in the composition in about 5000 U.

76. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor is isolated or purified from human plasma.

77. The pharmaceutical composition of claim 76, wherein the C1 esterase inhibitor isolated or purified from human plasma is nanofiltered.

78. The pharmaceutical composition of claim 76, wherein the C1 esterase inhibitor isolated or purified from human plasma is pasteurized.

79. The pharmaceutical composition of claim 63 or 64, wherein the pharmaceutical composition is prepared in liquid form.

80. The pharmaceutical composition of claim 63 or 64, wherein the pharmaceutical composition is reconstituted with water from at least one lyophilized powder.

81. The pharmaceutical composition of claim 63 or 64, wherein the composition has a viscosity of less than about 20 mPa-s.

82. The pharmaceutical composition of claim 63 or 64, wherein the composition has a viscosity of less than about 10 mPa-s.

83. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor present in the composition comprises at least 50-60% of the total protein in the composition.

84. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor present in the composition comprises at least 75% of the total protein in the composition.

85. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than a 10% loss in monomer content when stored for two years at 4°C.

86. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 20% loss in monomer content loss when stored for one week at 40°C.

87. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 10% loss in monomer content loss when stored for two weeks at 25°C.

88. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 2% loss in purity when stored for one week at 40° C.

89. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 1% loss in purity when stored for one week at 40° C.

90. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 2% loss in purity when stored for two weeks at 25° C.

91. The pharmaceutical composition of claim 63 or 64, wherein the C1 esterase inhibitor has less than about 1% loss in purity when stored for two weeks at 25° C.

92. The pharmaceutical composition of claim 63 or 64, wherein the pharmaceutical composition is a monoformulation of active pharmaceutical ingredient, wherein said active pharmaceutical ingredient consists essentially of C1 esterase inhibitor.

C1-INH COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF DISORDERS ASSOCIATED WITH C1 ESTERASE INHIBITOR DEFICENCY

ABSTRACT

Compositions and methods for the treatment and/or prevention of disorders associated with C1 esterase inhibitor deficiency are disclosed.

[No suitable figure]