CLAIMS

1. A method of administering a therapeutic agent to a patient, comprising subcutaneously administering the therapeutic agent to the patient, such that the C_{max}:$C_{average}$ ratio is lower than the C_{max}:$C_{average}$ ratio of the agent when delivered intravenously, and wherein the therapeutic agent is modified in order to increase the hydrophilicity and modify the molecular dimensions in relation to the native state of the therapeutic agent.

2. A method of administering a therapeutic agent to the lymphatic system of a patient, comprising the step of subcutaneously administering the therapeutic agent, such that it does not directly enter the circulatory system of the patient at the site of injection, and wherein the therapeutic agent is modified in order to increase the hydrophilicity and modify the molecular dimensions in relation to the native state of the therapeutic agent.

3. A method of preventing entry of a therapeutic agent directly into the local circulatory system of a patient upon subcutaneous administration of the therapeutic agent to a patient, the method comprising the step of subcutaneously administering the modified agent to the patient and wherein the therapeutic agent is modified in order to increase the hydrophilicity and modify the molecular dimensions in relation to the native state of the therapeutic agent, such that the modified therapeutic agent is unable to enter the local vasculature directly from the site of administration.

4. A method of modulating the speed of delivery of a therapeutic agent from a subcutaneous depot in a subject, comprising modifying the therapeutic agent to alter the hydrophilicity of the agent, wherein the level of hydrophilicity is proportional to the level of bioavailability.

5. A method according to any one of claims 1 to 4, wherein the subcutaneous administration of the modified therapeutic agent enables a higher dose of the modified agent to be administered to the patient than can be safely delivered by a single intravenous bolus injection.

6. A method according to any one of claims 1 to 5, wherein the subcutaneous administration of the modified therapeutic agent enables the patient to be re-dosed earlier than if the modified agent is administered intravenously.

7. A method according to any one of claims 1 to 6, wherein the subcutaneous administration of the modified therapeutic agent produces a lesser or equivalent immunogenic response than the intravenous administration of the agent in its modified or native form.

8. A method according to any one of claims 1 to 7, wherein the hydrophilicity of the therapeutic agent is increased by at least 50% in relation to the native state of the therapeutic agent.

9. A method according to any one of claims 1 to 8, wherein the therapeutic agent is an antibiotic, a blood clotting factor, a hormone, another therapeutic peptide or protein, a small molecule or a monoclonal antibody.

10. The method according to claim 9, wherein the blood clotting factor is selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor, and Protein C.

11. A method according to any one of claims 1 to 10, wherein the modification is conjugation of the therapeutic agent to a biocompatible polymer.

12. The method according to claim 11, wherein the biocompatible polymer is polyethylene glycol (PEG), poly-phosphatidyl choline (PC), polypropylene glycol (PPG), copolymers of ethylene glycol and propylene glycol, polyethylene oxide (PEO), polyoxyethylated polyol, polyolefinic alcohol, polyhydroxyalkylmethacrylate, polysaccharides, poly α-hydroxy acid, polyvinyl alcohol, polyphosphosphasphazene, poly N-acryloylmorpholine, polyalkyene oxide polymers, polymaleic acid, poly DL-alanine, carboxymethylcellulose, dextran, starch or starch derivatives, hyaluronic acid chitin, polymethacrylates, polysialic acid (PSA), polyhydroxy alkanoates, poly amino acids and combinations thereof.

13. The method according to claim 11 or 12, wherein the biocompatible polymer is PEG

14. A method according to any one of claims 1 to 13, wherein the modification is a fusion to a polypeptide to produce a fusion protein; incorporation into vesicular delivery vehicles such as liposomes, transfersomes or micelles; incorporation into or attachment to dendrimers or the formation of oligomer complexes of the therapeutic agent.

15. A method according to any one of claims 1 to 14, wherein the subcutaneous delivery volume of the therapeutic agent is no more than 2ml.

16. A method according to any one of claims 1 to 15, wherein the modified therapeutic agent is deliverable at a concentration higher than the concentration of the modified agent than can be safely delivered intravenously.

17. A method according to any one of claims 1 to 16, wherein subcutaneous delivery of the modified therapeutic agent provides a therapeutic benefit to the patient for a duration of at least 12 hours longer than the therapeutic benefit of the modified agent when administered intravenously.

18. A method according to any one of claims 1 to 17, wherein the subcutaneous delivery is by subcutaneous injection, topical application, transdermal patch, microdermal abrasion, or high pressure dry powder delivery.

19. A method according to any one of claims 1 to 18, wherein the subcutaneous delivery is at least once per day, at least twice per day, at least once per week, at least twice per week, at least once per two weeks or at least once per month.

20. A modified agent comprising a therapeutic agent and a modification, wherein the modification increases the hydrophilicity and modifies the molecular dimensions of the agent in relation to the native state of the therapeutic agent for use in a method according to any one of claims 1 to 19.

21. A modified agent for use according to claim 19, wherein the modification increases the hydrophilicity of the agent by at least 50% in relation to the native state of the therapeutic agent.

22. A modified agent as claimed in claim 20 or in claim 21, in which the modification is a biocompatible polymer fused to the therapeutic agent.

23. A modified agent as claimed in any one of claims 20 to 22, wherein subcutaneous delivery of the modified agent provides a therapeutic benefit to the patient for a duration of at least 12 hours longer than the therapeutic benefit of the modified agent when administered intravenously.

24. A dosage form of a pharmaceutical composition of a modified therapeutic agent, wherein subcutaneous delivery of the modified agent provides a therapeutic benefit to the patient for a duration of at least 12 hours longer than the therapeutic benefit of the modified agent when administered intravenously.

25. A dosage form of a pharmaceutical composition of a modified blood coagulation factor for subcutaneous administration which when formulated for subcutaneous administration to a patient provides a no more than once per month dosage form sufficient to maintain a whole blood clotting time in said patient of no more than 20 minutes.

26. A liquid dosage form of a PEGylated blood coagulation factor for subcutaneous administration no more than once per month wherein the dosage form has a C_{max} of at least 10% and no more than 90% compared to an equivalent reference dosage form when administered intravenously, for use in the treatment of a blood clotting disorder.

27. A dosage form according to any one of claims 24 to 26, wherein the dosage form provides a no more than once per fortnight, no more than once per week, no more than once per half week, no more than once per two days or no more than once per day dosage.

28. A dosage form according to any one of claims 24 to 26, wherein the dosage form is sufficient to maintain a whole blood clotting time in said patient of less than 15 minutes.

29. A dosage form according to any one of claims 24 to 26, wherein the dosage form is sufficient to maintain a whole blood clotting time in said patient of less than 12 minutes.

30. A dosage form as claimed in any one of claims 24 to 29, in which the blood clotting factor is selected from the group consisting of Factor VIIa, Factor VII, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C.

31. A dosage form as claimed in any one of claims 24 to 30, wherein the modification is PEGylation.

32. The dosage form as claimed in any one of claims 24 to 31 in which the dosage form has a C_{max} of at least 10% and no more than 90% compared to an equivalent reference dosage form when administered intravenously.

33. The dosage form as claimed in claim 32 in which the formulation has a C_{max} of from 10% to 20% compared to an equivalent reference dosage form when administered intravenously.

34. The dosage form as claimed in claim 33, wherein the agent is Factor VIII.

35. The dosage form as claimed in claim 32 in which the formulation has a C_{max} of from 40% to 60% compared to an equivalent reference dosage form when administered intravenously.

36. The dosage form as claimed in claim 35, wherein the agent is Factor IX.

37. The dosage form as claimed in claim 32 in which the formulation has a C_{max} of from 75% to 80% compared to an equivalent reference dosage form when administered intravenously.

38. The dosage form according to claim 32 in which the formulation has a C_{max} of 75% compared to an equivalent reference dosage form when administered intravenously.

39. The dosage form as claimed in claim 37 or claim 38, wherein the agent is Factor VII.

40. A dosage formulation according to any one of claims 24 to 39, in which the dosage is of from 1 to 1000 IU/kg.

41. A dosage formulation according to any one of claims 24 to 39 in which the dosage is of from 5 to 500 IU/kg.

42. A dosage formulation according to any one of claims 24 to 39, in which the dosage is of from 100 to 250 IU/kg.

43. A dosage formulation according to any one of claims 24 to 39, in which the dosage is of from 50 to 200 IU/kg.

44. A dosage formulation according to any one of claims 24 to 39, in which the dosage is of from 25 to 50 IU/kg.

45. A dosage formulation according to any one of claims 24 to 39, wherein the dosage form is for administration at least once per day, at least twice per day, about once per week, about twice per week, about once per two weeks, or about once per month.

46. A dosage formulation of a therapeutic agent wherein the dosage form is for subcutaneous administration and wherein the therapeutic agent is modified to alter the hydrophilicity of the agent, wherein the level of hydrophilicity is proportional to the level of bioavailability.

47. A method of treatment of a disease in a patient, comprising administering subcutaneously a dosage form of a modified therapeutic agent according to claim 24.

48. A method of treatment of a blood clotting disease or trauma in a patient comprising administering subcutaneously a dosage form of a blood clotting factor according to any one of claims 24 to 46 to a patient in need thereof.

49. A method of treatment according to claim 47 or claim 48, wherein the dosage form is administered at least once per day, at least twice per day, at least about twice per week, at least about once per week, at least once per two weeks, or at least about once per month.

50. A method of treatment according to claim 47 or claim 48, wherein the dosage form is administered at least once per day.

51. A method of treatment according to claim 50, wherein the dosage form is administered twice per day, in which the patient receives a first dosage form in a first administration and a second dosage form in a second administration.

52. A method of treatment according to claim 51, wherein the second dosage form is administered separately, simultaneously or sequentially to the first dosage form.

53. A kit of parts comprising a subcutaneous dosage form according to any one of claims 24 to 46, and an administration vehicle.

5

CLAIMS

1. A subcutaneous dosage form of a pharmaceutical composition of a blood coagulation factor selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C conjugated to a polyethylene glycol (PEG) molecule for use in the treatment of a blood clotting disease or trauma in a patient, in which the dosage form is administered to the patient at intervals whereby normal haemostasis is maintained and in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.

2. A dosage form according to Claim 1, in which the blood coagulation factor is Factor VIII.

3. A dosage form according to Claim 1, in which the blood coagulation factor is Factor IX.

4. A dosage form according to Claim 1, in which the blood coagulation factor is Factor VIIa.

5. A dosage form according to any preceding claim, in which the dosage form comprises an excipient.

6. A dosage form according to Claim 5, in which the excipient is selected from the group consisting of liposomes, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof.

7. A dosage form according to any preceding claim, in which the dosage of the blood coagulation factor is of from 1 to 1000 IU/kg.

8. A dosage form according to any of Claims 1 to 6, in which the dosage of the blood coagulation factor is of from 5 to 500 IU/kg.

9. A dosage form according to any of Claims 1 to 6, in which the dosage of the blood coagulation factor is of from 100 to 250 IU/kg.

10. A dosage form according to any of Claims 1 to 6, in which the dosage of the blood coagulation factor is of from 50 to 200 IU/kg.

11. A dosage form according to any of Claims 1 to 6, in which the dosage is from 25 to 50 IU/kg.

12. A dosage form according to any of Claims 1 to 6, in which the dosage is from 5 to 50 IU/kg.

13. A dosage form according to any of Claims 1 to 6, in which the dosage form is for administration at least once per day.

14. A dosage form according to Claim 13, in which the dosage form is administered twice per day, in which the patient receives a first dosage form in a first administration and a second dosage form in a second administration.

15. A dosage form according to Claim 14, in which the second dosage form is administered separately, simultaneously or sequentially to the first dosage form.

16. A dosage form of a blood coagulation factor according to any preceding claim for use in the treatment of a blood clotting disease or trauma.

17. A subcutaneous dosage form of a pharmaceutical composition of a blood coagulation factor selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C conjugated to a polyethylene glycol (PEG) molecule, in which the dosage of the blood coagulation factor is from 1 to 1000 IU/kg, and in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.

18. A subcutaneous dosage form comprising a PEGylated form of a therapeutic agent selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C, in which the PEG is directly or indirectly conjugated to the therapeutic agent; in which repeated subcutaneous administration of the dosage form to a subject before the concentration of the therapeutic agent in the blood reduces to sub-therapeutic levels provides a sustained therapeutic effect in the subject, in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl

residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.

19. A kit of parts comprising a dosage form according to any preceding claim, and an administration vehicle.

20. Use of a blood coagulation factor selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C conjugated to a polyethylene glycol (PEG) molecule in the preparation of a medicament for the treatment of a blood clotting disease or trauma in a patient, in which the medicament is in a subcutaneous dosage form, in which the dosage form is administered to the patient at intervals whereby normal haemostasis is maintained and in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.

21. Use of a blood coagulation factor selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C conjugated to a polyethylene glycol (PEG) molecule in the preparation of a subcutaneous dosage form of a pharmaceutical composition, in which the dosage of the blood coagulation factor is from 1 to 1000 IU/kg, and in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.

22. Use of a PEGylated form of a therapeutic agent selected from the group consisting of Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor Xa, Factor XI, Factor XIII, Factor V, von Willebrand's Factor and Protein C, in which the PEG is directly or indirectly conjugated to the therapeutic agent, in the preparation of a subcutaneous dosage form, in which repeated subcutaneous administration of the dosage form to a subject before the concentration of the therapeutic agent in the blood reduces to sub-therapeutic levels provides a sustained therapeutic effect in the subject, in which the PEG molecule is conjugated directly or indirectly to the blood coagulation factor via a serine or threonine residue, via a hydroxyl residue on a sugar residue, via a single cysteine residue, or via an amide, N-terminal amino group, or a carboxyl group.