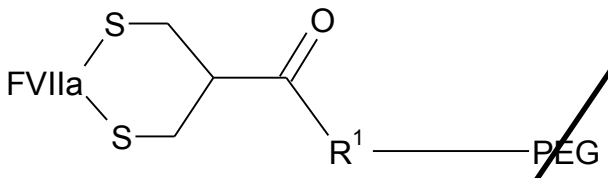
CLAIMS

1. A Factor VIIa-polyethylene glycol conjugate, in which one or more polyethylene glycol groups are conjugated to FVIIa by a linker group bridging the sulphur atoms of two cysteine residues that formed a disulphide bond in FVIIa, in which the conjugate has the structure:



in which R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the polymer is by a hydrolytically labile bond, or by a nonlabile bond.

2. A Factor VIIa-polyethylene glycol conjugate according to Claim 1, in which the polyethylene glycol has a molecular weight of about 5-100kDa.

3. A pharmaceutical composition comprising a Factor VIIa-polyethylene glycol conjugate as claimed in any preceding claim.

4. A pharmaceutical composition according to Claim 3 in which the composition comprises a pharmaceutically acceptable diluent, adjuvant or carrier.

5. A pharmaceutical composition as claimed in Claims 3 or 4, further comprising another pharmaceutically active agent.

6. A pharmaceutical composition according to any of Claims 3 to 5, which is suitable for parenteral administration.

7. A pharmaceutical composition according to any of Claims 3 to 6, which is suitable for intradermal, subcutaneous, and intramuscular injections, and intravenous or intraosseous infusions.

8. A pharmaceutical composition according to any of Claims 3 to 7 in the form of a solution, suspension or emulsion.

9. A pharmaceutical composition according to any of Claims 3 to 8, in which the FVIIa conjugate has a longer half-life as compared to unmodified FVIIa.

10. A pharmaceutical composition according to any of Claims 3 to 9, in which the FVIIa conjugate has a higher AUC as compared to unmodified FVIIa.

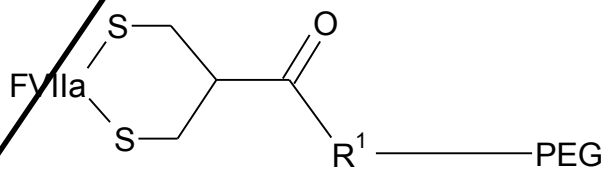
11. A pharmaceutical composition according to any of Claims 3 to 10, in which the FVIIa conjugate has a higher bioavailability as compared to unmodified FVIIa.

12. A pharmaceutical composition according to any of Claims 3 to 10, in which the FVIIa conjugate has a lower immunogenicity as compared to unmodified FVIIa.

13. A Factor VIIa-polyethylene glycol conjugate according to Claim 1 or Claim 2 for use in the treatment of a blood clotting disease characterised by a loss of function of FVIIa, or for use in the treatment of trauma.

14. Use of a Factor VIIa-polyethylene glycol conjugate according to Claim 1 or Claim 2 in the preparation of a medicament for the treatment of a blood clotting disease characterised by a loss of function of FVIIa, or in the preparation of a medicament for the treatment of trauma.

15. A process for preparing the following Factor VIIa-polyethylene glycol conjugate,



in which R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the polymer is by a hydrolytically labile bond, or by a nonlabile bond, and in which the process comprises:

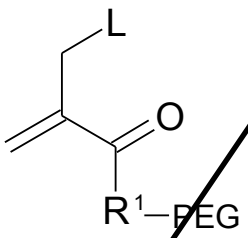
(a) reduction of a native disulphide bond between two cysteine residues in FVIIa, to generate two free thiol groups;

(b) a first thiolate addition reaction between a conjugation-reagent comprising a conjugated double bond and a leaving group;

(c) elimination of the leaving group, generating a conjugated double bond; and

(d) a second thiolate addition reaction, forming a 3-carbon bridge between the two sulphur atoms.

16. A process according to Claim 15, in which the conjugation reagent has the formula

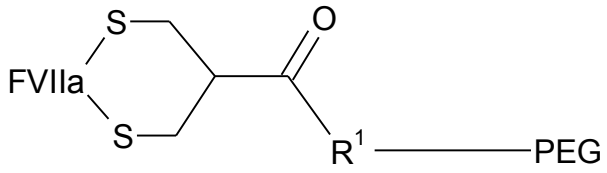


where R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the polymer is by a hydrolytically labile bond, or by a nonlabile bond, and L is a leaving group.

17. A Factor VIIa-polyethylene glycol conjugate, pharmaceutical composition, use or process substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.

CLAIMS

1. A Factor VIIa-polyethylene glycol conjugate, in which one or more polyethylene glycol (PEG) groups are conjugated to FVIIa by a linker group bridging the sulphur atoms of two cysteine residues that formed a disulphide bond in FVIIa, in which the conjugate has the structure:



in which R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the PEG is by a hydrolytically labile bond, or by a nonlabile bond.

2. A Factor VIIa-polyethylene glycol conjugate according to Claim 1, in which the polyethylene glycol has a molecular weight of about 5-100kDa.

3. A pharmaceutical composition comprising a Factor VIIa-polyethylene glycol conjugate according to Claim 1 or Claim 2.

4. A pharmaceutical composition according to Claim 3 in which the composition comprises a pharmaceutically acceptable diluent, adjuvant or carrier.

5. A pharmaceutical composition according to Claim 3 or 4, further comprising another pharmaceutically active agent.

6. A pharmaceutical composition according to Claim 3, 4 or 5, which is suitable for parenteral administration.

7. A pharmaceutical composition according to any of Claims 3 to 6, which is suitable for intradermal, subcutaneous, and intramuscular injections, and intravenous or intraosseous infusions.

8. A pharmaceutical composition according to any of Claims 3 to 7 in the form of a solution, suspension or emulsion.

9. A Factor VIIa-polyethylene glycol conjugate according to Claim 1 or Claim 2 for use in the treatment of a blood clotting disease characterised by a loss of function of FVIIa, or for use in the treatment of trauma.

10. A pharmaceutical composition according to any of Claims 3 to 8 for use in treating a blood clotting disease or trauma.

11. A Factor VIIa-polyethylene glycol conjugate for use according to Claim 9 or a pharmaceutical composition according to Claim 10, in which the blood clotting disease is haemophilia A or haemophilia B.

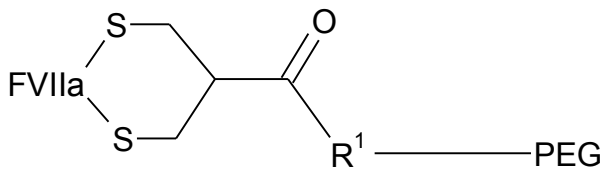
12. A pharmaceutical composition comprising a FVIIa conjugate according to any of Claims 5 to 8 for use in reducing the risk of hemarthrosis, hemorrhage, gastrointestinal bleeding and menorrhagia in mammals with haemophilia A, haemophilia B or trauma.

13. A pharmaceutical composition for use according to Claim 12, in which the composition is for subcutaneous administration.

14. A pharmaceutical composition for use according to Claim 12, in which the composition is for intravenous administration.

15. A pharmaceutical composition for use according to Claim 12, in which the composition is for administration once every one to fourteen days.

16. A process for preparing the following Factor VIIa-polyethylene glycol conjugate,



in which R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include

pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the polymer is by a hydrolytically labile bond, or by a nonlabile bond, and in which the process comprises:

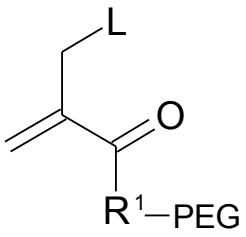
(a) reduction of a native disulphide bond between two cysteine residues in FVIIa, to generate two free thiol groups;

(b) a first thiolate addition reaction between a conjugation-reagent comprising a conjugated double bond and a leaving group;

(c) elimination of the leaving group, generating a conjugated double bond; and

(d) a second thiolate addition reaction, forming a 3-carbon bridge between the two sulphur atoms.

17. A process according to Claim 16, in which the conjugation reagent has the formula



where R1 is a substituent which is a direct bond, an alkylene group (preferably a C_{1-10} alkylene group), or an optionally-substituted aryl or heteroaryl group; in which the aryl groups include phenyl, benzoyl and naphthyl groups; in which suitable heteroaryl groups include pyridine, pyrrole, furan, pyran, imidazole, pyrazole, oxazole, pyridazine, pyrimidine and purine; in which linkage to the polymer is by a hydrolytically labile bond, or by a nonlabile bond, and L is a leaving group.

18. A Factor VIIa-polyethylene glycol conjugate substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.

19. A pharmaceutical composition comprising a Factor VIIa-polyethylene glycol conjugate substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.

20. A Factor VIIa-polyethylene glycol conjugate for use in the treatment of a blood clotting disease characterised by a loss of function of FVIIa, or for use in the treatment of trauma substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.

21. A pharmaceutical composition comprising a Factor VIIa-polyethylene glycol conjugate for use in reducing the risk of hemarthrosis, hemorrhage, gastrointestinal bleeding and menorrhagia in mammals with haemophilia A, haemophilia B or trauma substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.

22. A process for preparing a Factor VIIa-polyethylene glycol conjugate substantially as hereinbefore described with reference to and as shown in Figures 1 to 16 of the accompanying drawings.