acid residues corresponding to the region of amino acid residues between Gly-289 and Asp-320, preferably between His-311 and Asp-320 of SEQ ID NO: 1; wherein the alteration is an insertion of at least one amino acid residue, which altered protein has a decreased sensitivity to inhibition by a direct Factor Xa inhibitor.

In another aspect, there is provided a nucleic acid molecule comprising a DNA sequence that encodes the protein as described herein.

In yet another aspect, there is provided an expression vector comprising the nucleic acid molecule as described herein.

In yet another aspect, there is provided a host cell comprising the nucleic acid molecule as described herein or the expression vector as described herein.

In yet another aspect, there is provided a pharmaceutical composition comprising the protein as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also disclosed is a method of completely or partially reversing an anti-coagulant effect of a coagulation inhibitor in a subject, said method comprising administering to said subject a therapeutically effective amount of the protein as described herein or the pharmaceutical composition as described herein.

In yet another aspect, there is provided use of the protein as described herein, for the manufacture of a medicament for completely or partially reversing an anti-coagulant effect of a direct Factor Xa inhibitor in a subject.

Detailed Description

The present invention solves this problem by providing, as an adequate reversal strategy to prevent and stop potential life-threatening bleeding complications

Claims

1. A recombinant protein comprising a coagulation factor Xa polypeptide, said polypeptide having an alteration in a region of amino acid residues corresponding to the region of amino acid residues between Gly-289 and Asp-320, preferably between His-311 and Asp-320 of SEQ ID NO: 1; wherein the alteration is an insertion of at least one amino acid residue, which altered protein has a decreased sensitivity to inhibition by a direct Factor Xa inhibitor.

2. The protein according to claim 1, wherein the insertion is 1-50 amino acid residues.

3. The protein according to claim 1 or claim 2, wherein the insertion is 1-20 amino acid residues.

4. The protein according to any one of claim 1-3, wherein said insertion is between two amino acid residues corresponding to Lys-316 and Glu-317 of SEQ ID NO: 1.

5. The protein according to any one of claims 1-4, wherein the insertion of at least one amino acid residue is combined with a replacement of between 1-8 amino acid residues in the region of amino acid residues between Gly-289 and Asp-320, preferably between His-311 and Asp-320 of SEQ ID NO: 1.

6. The protein according to any one of claims 1-5, wherein said insertion is 9-13 amino acid residues.

7. The protein according to any one of claims 1-6, wherein the region of amino acid residues corresponding to the region of amino acid residues between His-311 and Asp-320 of SEQ ID NO: 1 has the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 9, SEQ ID NO: 10, or SEQ ID NO: 11.

8. A nucleic acid molecule comprising a DNA sequence that encodes the protein according to any one of claims 1-7.

9. An expression vector comprising the nucleic acid molecule according to claim 8.

10. A host cell comprising the nucleic acid molecule according to claim 8 or the expression vector according to claim 9.

11. A pharmaceutical composition comprising the protein according to any of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. The protein according to any one of claims 1-9, or the pharmaceutical composition according to claim 11, for use as a medicament.

13. The protein according to any one of claims 1-9, or the pharmaceutical composition according to claim 11 for use in a method of completely or partially reversing an anti-coagulant effect of a coagulation inhibitor in a subject.

14. Use of the protein of any one of claims 1-7, for the manufacture of a medicament for completely or partially reversing an anti-coagulant effect of a direct Factor Xa inhibitor in a subject.

15. The use according to claim 14, wherein the direct factor Xa inhibitor, is rivaroxaban (5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]-2-thiophenecarboxamide), apixaban (1-(4methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide), edoxaban (N'-(5-chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4H-[1,3]thiazolo[5,4-c]pyridine-2-carbonyl)amino]cyclohexyl]oxamide;4-methylbenzenesulfonic acid), or betrixaban

(N-(5-chloropyridin-2-yl)-2-[[4-(N,N-dimethylcarbamimidoyl)benzoyl]amino]-5-methoxybenzamide).