Claims

1. A blood coagulation factor replacement product
   (i) for use in the treatment or prophylaxis of bleedings of patients having an acquired coagulation factor deficiency or
   (ii) for use in the treatment or prophylaxis of bleedings of patients having a congenital deficiency of a coagulation factor;
   said product comprising at least isolated prothrombin (Factor II) and isolated Antithrombin III (ATIII), wherein the molar ratio between ATIII to Factor II is at least 1 : 30;
   and wherein by administration of said product the patient's risk for a thromboembolic complication is reduced.

2. The blood coagulation factor replacement product for use according to claim 1, wherein by administration of said product the patient's risk for a thromboembolic complication is reduced compared to a reference treatment, said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

3. The blood coagulation factor replacement product for use according to claim 1 or claim 2, wherein the product further comprises at least one of isolated coagulation factors selected from the group consisting of Factor IX, Factor X and Factor VII.

4. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the amount of blood loss of the patient following the treatment with the product is decreased compared to an amount of blood loss following a placebo treatment or without treatment, wherein the amount of blood loss is preferably reduced to an amount of below 75%, below 70%, below 60%, below 55%, below 50%, below 45%, below 40% or below 35% of the amount following placebo treatment or of the amount without treatment.

5. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the amount of blood loss of the patient following the treatment with the product is either essentially identical or only moderately increased when compared

to a reference treatment, or wherein the amount of blood loss of the patient following the treatment with the product is decreased when compared to a reference treatment, preferably, the amount of blood loss of the patient following the treatment with the product being decreased when compared to a reference treatment by at least 5%, at least 10%, at least 15% or at least 20%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

6. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein in case of the amount of blood loss of the patient following the treatment with the product is only moderately increased when compared to an amount of blood loss of a reference treatment, said moderate increase amounting to not more than 60%, not more than 50%, not more than 40%, not more than 30%, not more than 20%, not more than 15%, not more than 10% or not more than 5%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

7. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of time to hemostasis of the patient following the treatment with the product is decreased compared to the value of time to hemostasis following placebo treatment or without treatment, wherein said value of time to hemostasis following treatment with the product is preferably decreased by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55% or at least 60% compared of the value following placebo treatment or of the value without treatment.

8. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of time to hemostasis of the patient following the treatment with the product is either essentially identical or only moderately increased when compared to a reference treatment, or wherein the value of time to hemostasis of the patient following the treatment with the product is decreased when compared to a reference treatment, preferably, the value of time to hemostasis of the patient following the treatment with the product being decreased compared to a value following a reference treatment by at least 5%, by at least 10%, by at least 15% or by at least 20%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

9. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein in case of the value of time to hemostasis of the patient following the treatment with the product is only moderately increased when compared to a reference treatment, said moderate increase of the value amounting to not more than 80%, not more than 70%, not more than 60%, not more than 50%, not more than 40%, not more than 30%, not more than 20% or not more than 10%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

10. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of the patient following the treatment with the product is decreased compared to the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of a reference treatment by a factor of at least 1.5, at least 2.0, at least 2.5, at least 3.0, at least 3.5, at least 4.0, at least 4.5, at least 5.0, at least 7, or at least 10, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

11. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of the patient following the treatment with the product is essentially identical and/or has a maximum deviation of said value when compared to the respective value of prothrombin time (PT) and/or the respective value of activated partial thromboplastin time (aPTT) following placebo treatment or without treatment, provided that said maximum deviation does not exceed a factor of 5.0, of 3.0, of 2.5, of 2.0, or of 1.5.

12. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of thrombin generation, in particular of the Endogenous Thrombin Potential (ETP), of the patient following the treatment with the product is reduced when compared to a value of thrombin generation, in particular of the Endogenous Thrombin Potential (ETP), of a reference treatment by at least 5%, by at least 10%, by at least 15%, by at least 20%, by at least 25%, by at least 30%, by at least 35%, by at least 40%, by at least 45% or by at least 50%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

13. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the value of D-Dimer concentration (DD) of the patient's blood following the treatment with the product is reduced compared to a reference treatment by a factor of at least 2, at least 3, at least 4, at least 5, at least 7, or at least 10, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

14. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the product further comprises heparin and/or albumin.

15. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the factor II is provided within the product with an activity level of between 10 – 80 IU/mL, preferably between 15 – 60 IU/mL.

16. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the molar ratio between ATIII to Factor II is not higher than 1 : 0.5, preferably not higher than 1 : 1.

17. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein the molar ratio between ATIII to Factor II is within a range between 1 : 25 to 1 : 0.5, preferably between 1 : 25 to 1 : 1.

18. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein said treatment or prophylaxis comprises treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, in particular a deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required; or wherein said treatment or prophylaxis comprises treatment and perioperative prophylaxis of bleedings in congenital deficiency of any vitamin K dependent coagulation factor, in particular, when purified specific coagulation factor products are not available.

19. The blood coagulation factor replacement product for use according to any one of the preceding claims, wherein in addition to the treatment with said product the patient is in advance, simultaneously or subsequently treated with a replacement product, such as cryoprecipitate, or with a fibrinogen concentrate, preferably the replacement product or the

fibrinogen concentrate being administered at a fibrinogen amount in a range between 5 mg/kg and 150 mg/kg bodyweight, between 10 mg/kg and 100 mg/kg bodyweight, preferably between 20 mg/kg and 80 mg/kg bodyweight.

20. The blood coagulation factor replacement product for use according to any one of claims 3 to 19, wherein the product is a prothrombin complex concentrate (PCC) of either one of the following two types:
    - a 3-factor complex comprising factors II, IX and X; or
    - a 4-factor complex additionally comprising factor VII;

    said product additionally comprises Antithrombin III (ATIII), wherein the molar ratio between ATIII to Factor II is at least 1 : 30.

21. A combination therapy comprising administration of a prothrombin complex concentrate (PCC) and co-administration of Antithrombin III (ATIII)
    (i) for treatment or prophylaxis of bleedings of patients having an acquired coagulation factor deficiency or
    (ii) for treatment or prophylaxis of bleedings of patients having a congenital deficiency of a coagulation factor,

    the PCC comprising at least prothrombin (Factor II), Factor IX, Factor X and optionally Factor VII, provided that the molar ratio between administered ATIII to administered Factor II is of at least 1 : 30; and

    wherein by administration of said combination the patient's risk for a thromboembolic complication is reduced.

22. A pharmaceutical blood coagulation factor replacement kit for use according to any one of claims 1 to 19, the kit comprising
    (i) a first composition comprising at least prothrombin (Factor II) and
    (ii) a second composition comprising Antithrombin III (ATIII), wherein said first composition and said second composition are provided within the kit in order to allow either
        (a) prior to administration for preparation of a mixture, having a molar ratio between ATIII to Factor II of at least 1 : 30 and/or
        (b) for co-administration of said mixture or compositions, provided that the molar ratio between administered ATIII to administered Factor II is of at least 1 : 30, wherein by administration of said compositions the patient's risk for a thromboembolic complication is reduced.

23. A pharmaceutical product comprising Antithrombin III (ATIII) for co-administration with a prothrombin (Factor II) comprising product

(i) for use in the treatment or prophylaxis of bleedings of patients having an acquired coagulation factor deficiency or

(ii) for use in the treatment or prophylaxis of bleedings of patients having a congenital deficiency of a coagulation factor;

wherein prothrombin (Factor II) and Antithrombin III (ATIII) are co-administered having a molar ratio between ATIII to Factor II of at least 1 : 30;

and wherein by co-administration of said products the patient's risk for a thromboembolic complication is reduced.

24. A method of

(i) treatment or prophylaxis of bleedings of patients having an acquired coagulation factor deficiency or

(ii) treatment or prophylaxis of bleedings of patients having a congenital deficiency of a coagulation factor;

by administering a blood coagulation factor replacement product to said patient,

said product comprising at least isolated prothrombin (Factor II) and isolated Antithrombin III (ATIII), wherein the molar ratio between ATIII to Factor II is at least 1 : 30;

and wherein by administration of said product the patient's risk for a thromboembolic complication is reduced.

Claims

1. Use of a blood coagulation factor replacement product in the preparation of a medicament for:
   (i) the treatment or prophylaxis of bleedings of patients having an acquired coagulation factor deficiency or
   (ii) the treatment or prophylaxis of bleedings of patients having a congenital deficiency of a coagulation factor;
   said product comprising at least isolated prothrombin (Factor II) and isolated Antithrombin III (ATIII), wherein the molar ratio between ATIII to Factor II is at least 1 : 30 and the molar ratio between ATIII to Factor II is not higher than 1 : 0.5;
   and wherein by administration of said product the patient's risk for a thromboembolic complication is reduced.

2. The use according to claim 1, wherein by administration of said product the patient's risk for a thromboembolic complication is reduced compared to a reference treatment, said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

3. The use according to claim 1 or claim 2, wherein the product further comprises at least one of isolated coagulation factors selected from the group consisting of Factor IX, Factor X and Factor VII.

4. The use according to any one of the preceding claims, wherein the amount of blood loss of the patient following the treatment with the product is decreased compared to an amount of blood loss following a placebo treatment or without treatment, wherein the amount of blood loss is preferably reduced to an amount of below 75%, below 70%, below 60%, below 55%, below 50%, below 45%, below 40% or below 35% of the amount following placebo treatment or of the amount without treatment.

5. The use according to any one of the preceding claims, wherein the amount of blood loss of the patient following the treatment with the product is either essentially identical or only moderately increased when compared to a reference treatment, or wherein the amount of blood loss of the patient following the treatment with the product is decreased when compared to a reference treatment, preferably, the amount of blood loss of the patient following the treatment with the product being decreased when compared to a reference treatment by at least 5%, at least 10%, at least 15% or at least 20%, wherein said reference

treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

6. The use according to any one of the preceding claims, wherein in case of the amount of blood loss of the patient following the treatment with the product is only moderately increased when compared to an amount of blood loss of a reference treatment, said moderate increase amounting to not more than 60%, not more than 50%, not more than 40%, not more than 30%, not more than 20%, not more than 15%, not more than 10% or not more than 5%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

7. The use according to any one of the preceding claims, wherein the value of time to hemostasis of the patient following the treatment with the product is decreased compared to the value of time to hemostasis following placebo treatment or without treatment, wherein said value of time to hemostasis following treatment with the product is preferably decreased by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55% or at least 60% compared of the value following placebo treatment or of the value without treatment.

8. The use according to any one of the preceding claims, wherein the value of time to hemostasis of the patient following the treatment with the product is either essentially identical or only moderately increased when compared to a reference treatment, or wherein the value of time to hemostasis of the patient following the treatment with the product is decreased when compared to a reference treatment, preferably, the value of time to hemostasis of the patient following the treatment with the product being decreased compared to a value following a reference treatment by at least 5%, by at least 10%, by at least 15% or by at least 20%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

9. The use according to any one of the preceding claims, wherein in case of the value of time to hemostasis of the patient following the treatment with the product is only moderately increased when compared to a reference treatment, said moderate increase of the value amounting to not more than 80%, not more than 70%, not more than 60%, not more than 50%, not more than 40%, not more than 30%, not more than 20% or not more than 10%,

wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

10. The use according to any one of the preceding claims, wherein the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of the patient following the treatment with the product is decreased compared to the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of a reference treatment by a factor of at least 1.5, at least 2.0, at least 2.5, at least 3.0, at least 3.5, at least 4.0, at least 4.5, at least 5.0, at least 7, or at least 10, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

11. The use according to any one of the preceding claims, wherein the value of prothrombin time (PT) and/or the value of activated partial thromboplastin time (aPTT) of the patient following the treatment with the product is essentially identical and/or has a maximum deviation of said value when compared to the respective value of prothrombin time (PT) and/or the respective value of activated partial thromboplastin time (aPTT) following placebo treatment or without treatment, provided that said maximum deviation does not exceed a factor of 5.0, of 3.0, of 2.5, of 2.0, or of 1.5.

12. The use according to any one of the preceding claims, wherein the value of thrombin generation, in particular of the Endogenous Thrombin Potential (ETP), of the patient following the treatment with the product is reduced when compared to a value of thrombin generation, in particular of the Endogenous Thrombin Potential (ETP), of a reference treatment by at least 5%, by at least 10%, by at least 15%, by at least 20%, by at least 25%, by at least 30%, by at least 35%, by at least 40%, by at least 45% or by at least 50%, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

13. The use according to any one of the preceding claims, wherein the value of D-Dimer concentration (DD) of the patient’s blood following the treatment with the product is reduced compared to a reference treatment by a factor of at least 2, at least 3, at least 4, at least 5, at least 7, or at least 10, wherein said reference treatment is identical to said treatment, except that the molar ratio between ATIII to Factor II of the product used in said reference treatment is below 1 : 30.

14. The use according to any one of the preceding claims, wherein the product further comprises heparin and/or albumin.

15. The use according to any one of the preceding claims, wherein the factor II is provided within the product with an activity level of between 10 – 80 IU/mL, preferably between 15 – 60 IU/mL.

16. The use according to any one of the preceding claims, wherein the molar ratio between ATIII to Factor II is not higher than 1 : 1.

17. The use according to any one of the preceding claims, wherein the molar ratio between ATIII to Factor II is within a range between 1 : 25 to 1 : 0.5, preferably between 1 : 25 to 1 : 1.

18. The use according to any one of the preceding claims, wherein said treatment or prophylaxis comprises treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, in particular a deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required; or wherein said treatment or prophylaxis comprises treatment and perioperative prophylaxis of bleedings in congenital deficiency of any vitamin K dependent coagulation factor, in particular, when purified specific coagulation factor products are not available.

19. The use according to any one of the preceding claims, wherein in addition to the treatment with said product the patient is in advance, simultaneously or subsequently treated with a replacement product, such as cryoprecipitate, or with a fibrinogen concentrate, preferably the replacement product or the fibrinogen concentrate being administered at a fibrinogen amount in a range between 5 mg/kg and 150 mg/kg bodyweight, between 10 mg/kg and 100 mg/kg bodyweight, preferably between 20 mg/kg and 80 mg/kg bodyweight.

20. The use according to any one of claims 3 to 19, wherein the product is a prothrombin complex concentrate (PCC) of either one of the following two types:
    - a 3-factor complex comprising factors II, IX and X; or
    - a 4-factor complex additionally comprising factor VII.

21. The use according to claims 1 to 20, said product comprising a prothrombin complex concentrate (PCC) and Antithrombin III (ATIII), wherein the PCC comprising at least

prothrombin (Factor II), Factor IX, Factor X and optionally Factor VII, provided that the molar ratio between ATIII to be administered to Factor II to be administered is of at least 1 : 30 and the molar ratio between ATIII to Factor II is not higher than 1 : 0.5; and wherein by administration of said combination the patient's risk for a thromboembolic complication is reduced.

22. The use according to any one of claims 1 to 19, wherein the medicament is provided in the form of a pharmaceutical kit comprising
    (i) a first composition comprising at least prothrombin (Factor II) and
    (ii) a second composition comprising Antithrombin III (ATIII), wherein said first composition and said second composition are provided within the kit in order to allow either
    (a) prior to administration for preparation of a mixture, having a molar ratio between ATIII to Factor II within a range of 1 : 30 and 1 : 0.5 and/or
    (b) for co-administration of said mixture or compositions, provided that the molar ratio between administered ATIII to administered Factor II is within a range between 1 : 30 and 1 : 0.5, wherein by administration of said compositions the patient's risk for a thromboembolic complication is reduced.

23. The use of claims 1 to 19, in the form of a pharmaceutical product for co-administration, wherein prothrombin (Factor II) and Antithrombin III (ATIII) are co-administered having a molar ratio between ATIII to Factor II of at least 1 : 30 and the molar ratio between ATIII to Factor II is not higher than 1 : 0.5;
    and wherein by co-administration of said products the patient's risk for a thromboembolic complication is reduced.