CLAIMS

1. An article of manufacture comprising:

a) a packaging material

b) a polypeptide of SEQ ID NO: 1 , or a biosimilar thereof, and

c) a label or package insert contained within said packaging material indicating that:

the polypeptide or biosimilar thereof should not be administered to patients with severe haemorrhage, and/or

the therapy should be discontinued in patients who experience gastrointestinal perforation, and/or

the therapy should be discontinued in patients with compromised wound healing.

2. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom.

3. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with Metastatic Colorectal Cancer (mCRC).

4. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

5. The article of manufacture according to claim 1 further comprising, in separate containers, (1) a pharmaceutical composition comprising the polypeptide, or biosimilar thereof, (2) a pharmaceutical composition comprising leucovorin, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinocetan.

6. The article of manufacture according to claim 5 wherein the pharmaceutical composition comprising the polypeptide is hyperosmolar.

7. The article of manufacture according to claim 5 wherein the osmolarity of the pharmaceutical composition comprising the polypeptide is higher than 500 mOsm.

8. The article of manufacture according to claim 5 wherein it contains sucrose, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium hydroxide and/or hydrochloric acid and water for injections.

9. The article of manufacture according to claim 1 wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof is sialilated.

10. The article of manufacture according to claim 1 wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof contains about 8 to 12 moles of sialic acid/moles of polypeptide.

11. The article of manufacture according to claim 1 wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof forms a dimer.

12. The article of manufacture according to claim 1 wherein the label or package insert contained within said packaging material further indicates that 4 mg/kg of the polypeptide, or biosimilar thereof, is administered as an intravenous infusion over 1 hour every 2 weeks.

13. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, should not be administered as an intravenous (IV) push or bolus.

14. The article of manufacture according to claim 1 further comprising single-use vials containing 100 mg/4 ml. of the polypeptide, or biosimilar thereof.

15. The article of manufacture according to claim 1 further comprising single-use vials containing 200 mg/8 ml. of the polypeptide, or biosimilar thereof.

16. An article of manufacture according to any one of claim 1 wherein said composition comprises aflibercept or ziv- aflibercept or a biosimilar thereof.

17. An article of manufacture according to claim 1 wherein said label or package insert comprises a printed statement comprising the following information:

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received ZALTRAP in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ZALTRAP to patients with severe hemorrhage [*see Dosage and Administration (2.2), Warnings and Precautions (5.1)*].

Gastrointestinal Perforation: Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Discontinue ZALTRAP therapy in patients who experience GI perforation [*see Dosage and Administration (2.2), Warnings and Precautions (5.2)*].

Compromised Wound Healing: Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

18. A method of promoting the use of a polypeptide of SEQ ID NO:1, or a biosimilar thereof, the method comprising the step of conveying to a recipient at least one message selected from the group consisting of:

a. the polypeptide, or biosimilar thereof, should not be administered to patients with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, should be discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, should be discontinued in patients with compromised wound healing.

19. A method of treating cancer or cancer symptom in a patient in need thereof, said method comprising assessing whether said patient presents severe haemorrhage, and, if not, administering to said patient a therapeutically effective amount of a polypeptide of SEQ ID NO:1 , or biosimilar thereof.

20. A method of treating cancer or cancer symptom in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of a polypeptide of SEQ ID NO: 1 , or biosimilar thereof, wherein:

a. the polypeptide, or biosimilar thereof, is not administered to patients with severe haemorrhage, and/or

b. the administration of the polypeptide, or biosimilar thereof, is discontinued in patients who experience gastrointestinal perforation, and/or

c. the administration of the polypeptide, or biosimilar thereof, is discontinued in patients with compromised wound healing.

21. A method of treating Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom in a patient in need thereof, said method comprising administering to said patient therapeutically effective amounts of a polypeptide of SEQ ID NO: 1 , or biosimilar thereof, leucovorin, 5-fluorouracil (5-FU) and irinotecan wherein:

the polypeptide, or biosimilar thereof, is not administered to patients with severe haemorrhage, and/or

the administration of the polypeptide, or biosimilar thereof, is discontinued in patients who experience gastrointestinal perforation, and/or

the administration of the polypeptide, or biosimilar thereof, is discontinued in patients with compromised wound healing.

22. A method according to claim 21 wherein said patient has already been treated for the CRC or CRC symptom.

23. A method according to any one of claims 19 or 20 wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery.

24. A method according to claim 21 wherein said patient has previously been treated with therapy based on oxaliplatin or bevacizumab.

25. A method according to any one of claims 23 and 24 wherein said prior therapy has failed.

26. A method according to claim 21 wherein CRC is a Metastatic CRC.

27. A method according to claim 21 wherein said method is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

28. A method according to claim 21 wherein leucovorin at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU) at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2 , irinotecan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and the polypeptide of SEQ ID NO: 1 , or biosimilar thereof, at a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

29. A method according to claim 21 wherein leucovorin at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinotecan at a dosage of about 180 mg/m^2 and the polypeptide of SEQ ID NO:1, or biosimilar thereof, at a dosage of about 4 mg/kg are administered to patient.

30. A method according to claim 21 wherein leucovorin is administered intravenously at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) is administered intravenously at a dosage of about 2800 mg/m^2, irinotecan is administered intravenously at a dosage of about 180 mg/m^2 and the polypeptide of SEQ ID NO: 1, or biosimilar thereof, is administered intravenously at a dosage of about 4 mg/kg and wherein the combination is administered every two weeks.

31 . A method according to claim 21 wherein the leucovorin, 5-fluorouracil (5-FU), irinotecan and the polypeptide of SEQ ID NO:1, or biosimilar thereof, are administered intravenously every two weeks for a period comprised between 9 and 18 weeks.

32. A method according to claim 19 wherein the leucovorin is administered intravenously immediately after the polypeptide or biosimilar administration.

33. A method according to any one of claims 16 to 27 wherein the leucovorin is administered intravenously immediately after the polypeptide or biosimilar administration over a period of about 2 hours.

34. A method according to claim 21 wherein the irinotecan is administered intravenously immediately after the polypeptide or biosimilar administration.

35. A method according to claim 21 wherein the irinotecan is administered intravenously immediately after the polypeptide or biosimilar administration over a period of about 90 minutes.

36. A method according to claim 21 wherein the 5-fluorouracil (5-FU) is administered immediately after the polypeptide or biosimilar administration.

37. A method according to claim 21 wherein a first quantity of 5-fluorouracil (5-FU) is administered intravenously immediately after the polypeptide or biosimilar administration and a second quantity of 5-FU is administered intravenously after the first quantity in continuous infusion.

38. A method according to claim 21 wherein about 400 mg/m^2 of 5-fluorouracil (5-FU) is administered intravenously over a period of 2 to 4 minutes after the polypeptide or biosimilar administration and wherein 2400 mg/m^2 of 5-FU is administered intravenously over almost 46 hours after the administration of the 400 mg/m^2 in continuous infusion.

39. A method according to claim 21 wherein the patient has liver metastases.

40. Polypeptide of SEQ ID NO: 1, or biosimilar thereof, for use in treating patients with cancer or cancer symptom wherein:

a. the polypeptide, or biosimilar thereof, should not be administered to patients with a with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, should be discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, should be discontinued in patients with compromised wound healing.

41. Polypeptide of SEQ ID NO: 1, or biosimilar thereof, according to claim 40 wherein the cancer and cancer symptom are respectively Colorectal Cancer (CRC) and Colorectal Cancer (CRC) symptom.

42. Polypeptide of SEQ ID NO: 1, according to claim 40 wherein said polypeptide is aflibercept or ziv- aflibercept or a biosimilar thereof.

43. Composition comprising therapeutically effective amounts of a polypeptide of SEQ ID NO:1, or biosimilar thereof, in combination with leucovorin or folinic acid, 5-fluorouracil (5-FU) and irinocetan and comprising a pharmaceutically acceptable carrier for use in treating patients with Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom wherein:

a. the polypeptide, or biosimilar thereof, should not be administered to patients with a with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, should be discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, should be discontinued in patients with compromised wound healing.

44. A method of managing the risk of hemorrhage, gastrointestional perforation and compromised wound healing to allow a safe and effective use of a regiment comprising a polypeptide of SEQ ID NO:1 , or biosimilar thereof, leucovorin, 5-fluorouracil (5-FU) and irinotecan in the treatment of patients with colorectal cancer (CRC), said method comprising,
a) assessing whether a patient presents severe haemorrhage, and, if not, administering to said patient said regiment;

b) monitoring said patient for signs of gastrointestional perforation or compromised wound healing; and

c) discontinuing the regiment if said signs appear.

CLAIMS

1. An article of manufacture comprising:

a) a packaging material

b) a polypeptide of SEQ ID NO: 1 , or a biosimilar thereof, wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof contains about 8 to 12 moles of sialic acid/moles of polypeptide and

c) a label or package insert contained within said packaging material indicating that:

the polypeptide or biosimilar thereof should not be administered to patients with severe haemorrhage, and/or

the therapy should be discontinued in patients who experience gastrointestinal perforation, and/or

the therapy should be discontinued in patients with compromised wound healing.

2. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom.

3. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with Metastatic Colorectal Cancer (mCRC).

4. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, in combination with leucovorin, 5-fluorouracil (5-FU) and irinotecan is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

5. The article of manufacture according to claim 1 further comprising, in separate containers, (1) a pharmaceutical composition comprising the polypeptide, or biosimilar thereof, (2) a pharmaceutical composition comprising leucovorin, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinocetan.

6. The article of manufacture according to claim 5 wherein the pharmaceutical composition comprising the polypeptide is hyperosmolar.

7. The article of manufacture according to claim 5 wherein the osmolarity of the pharmaceutical composition comprising the polypeptide is higher than 500 mOsm.

8. The article of manufacture according to claim 5 wherein it contains sucrose, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium hydroxide and/or hydrochloric acid and water for injections.

9. The article of manufacture according to claim 1 wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof is sialilated.

10. The article of manufacture according to claim 1 wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof forms a dimer.

11. The article of manufacture according to claim 1 wherein the label or package insert contained within said packaging material further indicates that 4 mg/kg of the polypeptide, or biosimilar thereof, is administered as an intravenous infusion over 1 hour every 2 weeks.

12. The article of manufacture according to claim 1 wherein the label or package insert further indicates that the polypeptide, or biosimilar thereof, should not be administered as an intravenous (IV) push or bolus.

13. The article of manufacture according to claim 1 further comprising single-use vials containing 100 mg/4 ml. of the polypeptide, or biosimilar thereof.

14. The article of manufacture according to claim 1 further comprising single-use vials containing 200 mg/8 ml. of the polypeptide, or biosimilar thereof.

15. An article of manufacture according to claim 5 wherein said composition comprises aflibercept or ziv- aflibercept or a biosimilar thereof.

16. An article of manufacture according to claim 1 wherein said label or package insert comprises a printed statement comprising the following information:

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received ZALTRAP in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ZALTRAP to patients with severe hemorrhage [*see Dosage and Administration (2.2), Warnings and Precautions (5.1)*].

Gastrointestinal Perforation: Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Discontinue ZALTRAP therapy in patients who experience GI perforation [*see Dosage and Administration (2.2), Warnings and Precautions (5.2)*].

Compromised Wound Healing: Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

17. Use of a polypeptide of SEQ ID NO:1, or a biosimilar thereof, in the manufacture of a medicament for treating cancer or cancer symptom,

18. Use of a polypeptide of SEQ ID NO:1, or a biosimilar thereof, in the manufacture of a medicament for treating cancer or cancer symptom, wherein:

a. the polypeptide, or biosimilar thereof, is not administered to patients with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, is discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, is discontinued in patients with compromised wound healing.

19. Use of a polypeptide of SEQ ID NO:1, or a biosimilar thereof, leucovorin, 5-fluorouracil (5-FU) and irinotecan, in the manufacture of a medicament for treating cancer or cancer symptom, wherein:

the polypeptide, or biosimilar thereof, is not administered to patients with severe haemorrhage, and/or

the polypeptide, or biosimilar thereof, is discontinued in patients who experience gastrointestinal perforation, and/or

the polypeptide, or biosimilar thereof, is discontinued in patients with compromised wound healing.

20. The use according to claim 19 wherein said patient has already been treated for the CRC or CRC symptom.

21. The use according to any one of claims 17 or 18 wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery.

22. The use according to claim 19 wherein said patient has previously been treated with therapy based on oxaliplatin or bevacizumab.

23. The use according to any one of claims 21 and 22 wherein said prior therapy has failed.

24. The use according to claim 19 wherein CRC is a Metastatic CRC.

25. The use according to claim 19 wherein said method is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

26. The use according to claim 19 wherein leucovorin at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU) at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2 , irinotecan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and the polypeptide of SEQ ID NO: 1 , or biosimilar thereof, at a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

27. The use according to claim 19 wherein leucovorin at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinotecan at a dosage of about 180 mg/m^2 and the polypeptide of SEQ ID NO:1, or biosimilar thereof, at a dosage of about 4 mg/kg are administered to patient.

28. The use according to claim 19 wherein leucovorin is administered intravenously at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) is administered intravenously at a dosage of about 2800 mg/m^2, irinotecan is administered intravenously at a dosage of about 180 mg/m^2 and the polypeptide of SEQ ID NO: 1, or biosimilar thereof, is administered intravenously at a dosage of about 4 mg/kg and wherein the combination is administered every two weeks.

29. The use according to claim 19 wherein the leucovorin, 5-fluorouracil (5-FU), irinotecan and the polypeptide of SEQ ID NO:1, or biosimilar thereof, are administered intravenously every two weeks for a period comprised between 9 and 18 weeks.

30. The use according to claim 19 wherein the leucovorin is administered intravenously immediately after the polypeptide or biosimilar administration.

31. The use according to claim 19 wherein the leucovorin is administered intravenously immediately after the polypeptide or biosimilar administration over a period of about 2 hours.

32. The use according to claim 19 wherein the irinotecan is administered intravenously immediately after the polypeptide or biosimilar administration.

33. The use according to claim 19 wherein the irinotecan is administered intravenously immediately after the polypeptide or biosimilar administration over a period of about 90 minutes.

34. The use according to claim 19 wherein the 5-fluorouracil (5-FU) is administered immediately after the polypeptide or biosimilar administration.

35. The use according to claim 19 wherein a first quantity of 5-fluorouracil (5-FU) is administered intravenously immediately after the polypeptide or biosimilar administration and a second quantity of 5-FU is administered intravenously after the first quantity in continuous infusion.

36. The use according to claim 19 wherein about 400 mg/m^2 of 5-fluorouracil (5-FU) is administered intravenously over a period of 2 to 4 minutes after the polypeptide or biosimilar administration and wherein 2400 mg/m^2 of 5-FU is administered intravenously over almost 46 hours after the administration of the 400 mg/m^2 in continuous infusion.

37. The use according to claim 19 wherein the patient has liver metastases.

38. Polypeptide of SEQ ID NO: 1, or biosimilar thereof, for use in treating patients with cancer or cancer symptom wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof contains about 8 to 12 moles of sialic acid/moles of polypeptide, and wherein:

a. the polypeptide, or biosimilar thereof, should not be administered to patients with a with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, should be discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, should be discontinued in patients with compromised wound healing.

39. Polypeptide of SEQ ID NO: 1, or biosimilar thereof, according to claim 38 wherein the cancer and cancer symptom are respectively Colorectal Cancer (CRC) and Colorectal Cancer (CRC) symptom.

40. Polypeptide of SEQ ID NO: 1, according to claim 38 wherein said polypeptide is aflibercept or ziv- aflibercept or a biosimilar thereof.

41. Composition comprising therapeutically effective amounts of a polypeptide of SEQ ID NO:1, or biosimilar thereof, wherein the polypeptide of SEQ ID NO: 1, or a biosimilar thereof contains about 8 to 12 moles of sialic acid/moles of polypeptide, in combination with leucovorin or folinic acid, 5-fluorouracil (5- FU) and irinocetan and comprising a pharmaceutically acceptable carrier for use in treating patients with Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom wherein:

a. the polypeptide, or biosimilar thereof, should not be administered to patients with a with severe haemorrhage, and/or

b. the polypeptide, or biosimilar thereof, should be discontinued in patients who experience gastrointestinal perforation, and/or

c. the polypeptide, or biosimilar thereof, should be discontinued in patients with compromised wound healing.

42. Use of a polypeptide of SEQ ID NO:1, or a biosimilar thereof in the manufacture of a medicament for managing the risk of hemorrhage, gastrointestinal perforation and compromised wound healing to allow a safe and effective use of a regimen comprising such a polypeptide, leucovorin, 5-fluorouracil (5-FU) and irinotecan for the treatment of patients with colorectal cancer (CRC).