Claims

1. An aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

2. The aqueous formulation for use of claim 1 comprising 200 U/ml to 650 U/mL of insulin glargine.

3. The aqueous formulation for use of claim 1 comprising 700 U/ml to 1000 U/mL of insulin glargine.

4. The aqueous formulation for use of claim 2 comprising 270 – 330 U/mL of insulin glargine [equimolar to 270 – 330 IU human insulin].

5. The aqueous formulation for use of claim 4 comprising 300 U/mL of insulin glargine [equimolar to 300 IU human insulin].

6. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

7. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient to be treated has a HbA1c value of at least 8% at the onset of treatment.

8. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient to be treated has an age of at least 60 years at the onset of treatment.

9. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient to be treated has a BMI of at least 30 kg/m^2 at the onset of treatment.

10. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient to be treated received a basal insulin directly prior to the treatment.

11. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient to be treated received a mealtime short-acting insulin directly prior to the treatment.

12. The aqueous pharmaceutical formulation for use of claim 10 or 11, wherein the patient to be treated has a pre-injection SMPG of at least 9 mmol/L at the onset of treatment.

13. The aqueous pharmaceutical formulation for use of claim 10 or 11, wherein the patient to be treated has a fasting plasma glucose concentration of at least 8 mmol/L at the onset of treatment.

14. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the formulation is administered once daily in the evening at a predetermined time.

15. The aqueous pharmaceutical formulation for use of any of the foregoing claims, wherein the patient additionally receives a mealtime short-acting insulin.

16. The aqueous pharmaceutical formulation for use of any of the foregoing claims comprising an analogue of exendin-4.

17. The aqueous formulation for use of claim 16, wherein the analogue of exendin-4 is selected from a group comprising lixisentatide, exenatide and liraglutide.

18. The aqueous formulation for use of claim 17 comprising 0.1 µg to 10 µg lixisenatide per U insulin glargine.

19. The aqueous formulation for use of claim 18 comprising 0.2 to 1 µg lixisenatide per U insulin glargine.

20. The aqueous formulation for use of claim 19 comprising 0.25 µg to 0.7 µg lixisenatide per U insulin glargine.

21. The aqueous formulation for use of any of the foregoing claims comprising one or more excipients selected from a group comprising zinc, m-cresol, glycerol, polysorbate 20 and sodium.

22. The aqueous formulation for use of claim 21 comprising 90 µg/mL zinc, 2.7 mg/mL m-cresol and 20 mg/ml glycerol 85%.

23. The aqueous formulation for use of claims 21 comprising 90 µg/mL zinc, 2.7 mg/mL m-cresol, 20µg/mL polysorbate 20 and 20 mg/mL glycerol 85%.

24. The aqueous formulation for use of any of the foregoing claims, wherein the pH is between 3.4 and 4.6.

25. The aqueous formulation for use of claim 24, wherein the pH is 4.

26. The aqueous formulation for use of claim 24, wherein the pH is 4.5.

27. The pharmaceutical formulation for use of any one of the claims 1 to 26, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

28. The pharmaceutical formulation for use of claim 27, wherein the Diabetes Mellitus Type II is not adequately controlled with at least one oral antihyperglycemic alone.

29. The pharmaceutical formulation for use of claim 28, wherein the at least one oral

antihyperglycemic is metformin.

30. The pharmaceutical formulation for use of claim 29, wherein a treatment with at least 1.5 g/day of metformin does not adequately control the Diabetes Mellitus.

31. The aqueous pharmaceutical formulation for use of any of the claims 27 to 30, administered in combination with at least one oral antihyperglycemic agent.

32. The aqueous pharmaceutical formulation for use of claim 31, wherein the at least one antihyperglycemic agent is metformin.

33. The aqueous pharmaceutical formulation for use of any one of the preceding claims, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

34. A method of treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition comprising insulin glargine in a concentration of 300 U/mL, wherein the treatment reduces the risk of nocturnal hypoglycemia.

35. The method of claim 34 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

36. The method of claim 34 wherein said pharmaceutical composition further comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine.

37. Use of an aqueous formulation according to any of the foregoing claims for the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia.

38. An aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the formulation is administered once daily to a patient, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

39. The aqueous formulation of claim 38 administered on at least three days per week with the time interval specified in claim 38.

40. The aqueous formulation of claim 38 administered on at least four days per week with the time interval specified in claim 38.

41. The aqueous formulation of any one of the claims 38 to 40, wherein the time interval from the previous administration is in the range of 25 h to 28 h or in the range of 20 h to 23 h.

42. The aqueous formulation of any one of the claims 38 to 41, wherein the time interval from the previous administration is in the range of 25 h to 27 h or in the range of 21 h to 23 h.

43. The aqueous formulation of any one of the claims 38 to 42, wherein the time interval from the previous administration is in the range of 25 h to 26.5 h or in the range of 21.5 h to 23 h.

44. The aqueous formulation for use of any one of the claims 38 to 43, comprising insulin glargine in an amount as defined in any one of the claims 2 to 5.

45. The aqueous formulation for use of any one of the claims 38 to 44, wherein the patient is defined as in any one of the claims 7 to 15.

46. The aqueous formulation for use of any one of the claims 38 to 45, further

comprising an analogue of exendin-4, as defined in any one of the claims 16 to 20.

47. The aqueous formulation for use of any one of the claims 38 to 46, further comprising one or more excipients as defined in any one of the claims 21 to 23.

48. The aqueous formulation for use of any one of the claims 38 to 47, having a pH as defined in any one of the claims 24 to 26.

49. The aqueous formulation for use of any one of the claims 38 to 48, wherein the treatment reduces the risk of nocturnal hypoglycaemia.

50. The aqueous formulation for use of claim 49, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

51. The aqueous formulation for use of any one of the claims 38 to 50, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

52. The aqueous formulation for use of claim 51, wherein the Diabetes Mellitus type II is not adequately controlled with a least one oral antihyperglycemic agent alone, as defined in any one of the claims 28 to 32.

53. A method of treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition comprising insulin glargine in a concentration of 300 U/mL, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

54. The method of claim 53 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

55. The method of claim 53 wherein said pharmaceutical composition further comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine.

56. Use of an aqueous formulation according to any of the foregoing claims for the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

57. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing claims, and a label or packaging material indicating that the formulation is administered once daily, and wherein the time interval from the previous administration is between 21 h and 27 h, and wherein the average time interval from the previous administration is about 24 h.

58. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing claims, and a label or packaging material indicating that the formulation can be given together with other anti-hyperglyaemic medicinal products.

59. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing claims, and a label or packaging material indicating that changing from a once-daily administration of a basal insulin products to a once daily administration of the formulation can be done unit-to-unit based on the previous basal insulin dose; and changing from twice daily administration of a basal insulin product to once-daily administration of the formulation, the recommended initial dose of the formulation is 80% of the total daily dose of basal insulin that is being discontinued.

60. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing claims, and a label or packaging material indicating that in case the formulation is given together with a substance that may enhance the blood-glucose-lowering effect of the formulation selected from a group comprising anti-hyperglycaemic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics, a dose adjustment of the formulation may be needed.

61. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing claims, and a label or packaging material indicating that in case the formulation is given together with a substance that may reduce the blood-glucose-lowering effect of the formulation selected from a group comprising corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors a dose adjustment of the formulation may be needed.

Claims

1. Use of a once-daily aqueous pharmaceutical formulation comprising 200 - 1000 U/mL [equimolar to 200 - 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in Type I or Type II Diabetes Mellitus, wherein the time interval from the previous administration is in the range of 24.5 hours to 28 hours or in the range of 20 hours to 23.5 hours on at least two days per week and wherein the average once daily time interval from the previous administration is 24 hours..
2. The use of claim 1 comprising 200 U/ml to 650 U/mL of insulin glargine.
3. The use of claim 1 comprising 700 U/ml to 1000 U/mL of insulin glargine.
4. The use of claim 2 comprising 270 - 330 U/mL of insulin glargine [equimolar to 270 - 330 IU human insulin].
5. The use of claim 4 comprising 300 U/mL of insulin glargine [equimolar to 300 IU human insulin].
6. The use of any of the foregoing claims, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.
7. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having a HbA1 c value of at least 8% at the onset of treatment.
8. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having an age of at least 60 years at the onset of treatment.
9. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having a BMI of at least 30 kg/m^2 at the onset of treatment.

10. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient receiving a basal insulin directly prior to the treatment.
11. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient receiving a mealtime short-acting insulin directly prior to the treatment.
12. The use of claim 10 or 11, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having SMPG of at least 9 mmol/L at the onset of treatment.
13. The use of claim 10 or 11, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of reducing nocturnal hypoglycemia in the patient having a fasting plasma glucose concentration of at least 8 mmol/L at the onset of treatment.
14. The use of any of the foregoing claims, wherein the patient additionally receives a mealtime short-acting insulin.
15. The use of any of the foregoing claims further comprising an analogue of exendin-4.
16. The use of claim 15, wherein the analogue of exendin-4 is selected from a group comprising lixisentatide, exenatide and liraglutide.
17. The use of claim 16 comprising 0.1 g to 10 g lixisenatide per U insulin glargine.
18. The use of claim 17 comprising 0.2 to 1 g lixisenatide per U insulin glargine.
19. The use of claim 18 comprising 0.25g to 0.7g lixisenatide per U insulin glargine.
20. The use of any of the foregoing claims comprising one or more excipients selected from a group comprising zinc, m-cresol, glycerol, polysorbate 20 and sodium.
21. The use of claim 20 comprising 90 pg/nriL zinc, 2.7mg/mL m-cresol and 20 mg/ml glycerol 85%.
22. The use of claim 21 comprising 90 pg/nriL zinc, 2.7mg/mL m-cresol, 20pg/ml_ polysorbate 20 and 20 mg/mL glycerol 85%.
23. The use of any of the foregoing claims, wherein the pH is between 3.4 and 4.6.
24. The use of claim 23, wherein the pH is 4.
25. The use of claim 24, wherein the pH is 4.5.

26. The use of any one of the claims 1 to 25, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

27. The use of claim 26, wherein the Diabetes Mellitus Type II is not adequately controlled with at least one oral antihyperglycemic alone.

28. The use of claim 27, wherein the at least one oral antihyperglycemic is metformin.

29. The use of claim 28, wherein a treatment with at least 1 .5 g/day of metformin does not adequately control the Diabetes Mellitus.

30. The use of any of the claims 26 to 29, administered in combination with at least one oral antihyperglycemic agent.

31. The use of claim 30, wherein the at least one antihyperglycemic agent is metformin.

32. The use of claim 1, wherein the once daily time interval is at least three days per week.

33. The use of claim 32, wherein the once daily time interval is at least four days per week.

34. The use of any one of the claims 32 to 33, wherein the time interval from the previous administration is in the range of 25 h to 28 h or in the range of 20 h to 23 h.

35. The use of any one of the claims 32 to 34, wherein the time interval from the previous administration is in the range of 25 h to 27 h or in the range of 21 h to 23 h.

36. The use of any one of the claims 32 to 35, wherein the time interval from the previous administration is in the range of 25 h to 26.5 h or in the range of 21 .5 h to 23 h.

37. The use of any one of the claims 32 to 36, comprising insulin glargine in an amount as defined in any one of the claims 2 to 5.

38. The use of any one of the claims 32 to 37, wherein the patient is defined as in any one of the claims 7 to 14.

39. The use of any one of the claims 32 to 38, further comprising an analogue of exendin-4, as defined in any one of the claims 15 to 19.

40. The use of any one of the claims 32 to 39, further comprising one or more excipients as defined in any one of the claims 20 to 22.

41. The use of any one of the claims 32 to 40, having a pH as defined in any one of the claims 23 to 25.

42. The use of claim 41, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

43. The use of any one of the claims 32 to 42, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

44. The use of claim 43, wherein the Diabetes Mellitus type II is not adequately controlled with a least one oral antihyperglycemic agent alone, as defined in any one of the claims 28 to 32.