glargine. This formulation would allow patients to inject the same number of units of insulin glargine at one third the volume of injection.
Both insulin glargine formulations, U100 and U300, were expected to provide the same insulin exposure and the same effectiveness, i.e. time profiles.

SUMMARY

In one aspect, there is provided an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

In another aspect, there is provided a use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

In another aspect, there is provided a use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for extending the duration of exposure of a long acting insulin in the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

In another aspect, there is provided a use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for reducing the incidence of hypoglycaemia in the treatment of Type I and Type II Diabetes Mellitus in a patient with a long acting insulin, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

In another aspect, there is provided a use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for providing a peakless long acting basal insulin in the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

In another aspect, there is provided a use of the aqueous formulation as described herein in the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus.

DETAILED DESCRIPTION

Exposure and activity of insulin glargine U300, the test (T) medication, was tested in non-diabetic healthy subjects in euglycemic clamps for equivalence in exposure and activity to Lantus U100, the approved reference (R) product. To account for the long duration of action of insulin glargine after subcutaneous administration 30 hours were selected. Exposure was assessed from insulin glargine concentration time profiles after subcutaneous administration while activity was simultaneously assessed as glucose utilization per unit insulin.

A replicate design allowed limiting the number of subjects for assessing bioequivalence and variability as recommended by the FDA guideline "Guidance for Industry, Statistical Approaches to Establishing Bioequivalence".

The respective clinical study was expected to establish equivalence in exposure and activity.

A dose of 0.4 U/kg was selected for this study; it corresponds to the average basal insulin dose in patients. In non-diabetic healthy subjects this dose produces a sizeable elevation in plasma insulin concentration and a lasting glucose lowering effect that can be quantified in euglycemic clamp settings.

The replicate design favoured by guidelines requires two replicate single dose injections of either IP (R: Lantus® U100, T: insulin glargine U300) in predefined four way cross-over sequences (RTTR or TRRT) as allotted by the randomization plan. This was executed in Periods (P) 1 - 4 at four different days. As a result, each subject received two replicate single subcutaneous doses of 0.4 U/kg Lantus® U100 (R) and

Claims:

1. An aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

2. The aqueous pharmaceutical formulation of claim 1 comprising 200 U/mL of insulin glargine.

3. The aqueous pharmaceutical formulation of claim 1 comprising 500 U/mL of insulin glargine.

4. The aqueous formulation of any one of the claims 1 to 3 comprising an analogue of exendin-4 selected from a group comprising lixisenatide, exenatide and liraglutide.

5. The aqueous formulation of claim 4 comprising 0.1 μg to 10 μg lixisenatide per U insulin glargine.

6. The aqueous formulation of claim 5 comprising 0.2 to 1 μg lixisenatide per U insulin glargine.

7. The aqueous formulation of claim 6 comprising 0.25 μg to 0.7 μg lixisenatide per U insulin glargine.

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

9. The aqueous formulation of claim 8 comprising 90 μg/mL zinc, 2.7 mg/mL m-cresol and 20 mg/mL glycerol 85%.

10. The aqueous formulation of claim 8 comprising 90 μg/mL zinc, 2.7 mg/mL m-cresol, 20 μg/mL polysorbate 20 and 20 mg/mL glycerol 85%.

11. The aqueous formulation of any one of the claims 1 to 10, wherein the pH is 4.

12. The aqueous formulation of any one of the claims 1 to 10, wherein the pH is 4.5.

13. Use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

14. The use of claim 13 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

15. The use of claim 13 wherein said pharmaceutical composition further comprises 0.1 μg to 10 μg lixisenatide per U insulin glargine.

16. Use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for extending the duration of exposure of a long acting insulin in the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

17. The use of claim 16 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

18. The use of claim 16 wherein said pharmaceutical composition further comprises 0.1 μg to 10 μg lixisenatide per U insulin glargine.

19. Use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for reducing the incidence of hypoglycaemia in the treatment of Type I and Type II Diabetes Mellitus in a patient with a long acting insulin, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

20. The use of claim 19 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

21. The use of claim 19 wherein said pharmaceutical composition further comprises 0.1 μg to 10 μg lixisenatide per U insulin glargine.

22. Use of an aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine in the manufacture of a medicament for providing a peakless long acting basal insulin in the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 200-500 U/mL being equimolar to 200-500 IU human insulin.

23. The use of claim 22 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

24. The use of claim 22 wherein said pharmaceutical composition further comprises 0.1 μg to 10 μg lixisenatide per U insulin glargine.

25. Use of the aqueous formulation according to any of the foregoing claims in the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus.