Title: DOSAGE REGIMEN FOR THE TREATMENT OF DIABETES

Abstract: This invention relates to a drug treatment regimen for the treatment of subjects suffering from diabetes mellitus. More particularly the invention provides a method of administration of a less frequent than daily dosage of a long-acting insulin analogue. The invention also provides a kit of parts comprising the long-acting insulin analogue for use according to the invention and instructions for use.
DOSAGE REGIMEN FOR THE TREATMENT OF DIABETES

TECHNICAL FIELD

This invention relates to a drug treatment regimen for the treatment of subjects suffering from diabetes mellitus. More particularly the invention provides a method of administration of a less frequent than daily dosage of a long-acting insulin analogue. The invention also provides a kit of parts comprising the long-acting insulin analogue for use according to the invention and instructions for use.

BACKGROUND ART

Diabetes is a lifelong condition that causes a person's blood sugar level to become too high. There are two main types of diabetes, referred to as diabetes mellitus type 1 and diabetes mellitus type 2.

Insulin is essential for maintaining normal metabolic regulation, and may - eventually - be used for the treatment of diabetes type 2. Insulin is usually administered by subcutaneous injections, with an associated discomfort with the injections required to maintain close control of blood glucose levels.

Compliance is crucial in the management of chronic diseases, and the greater the number of drug intakes, the worse is the compliance. In fact the failure of people to consistently take their medicines is considered one of the biggest obstacles to better patient outcomes, and the possibility of a once-weekly administration would greatly improve quality of life for many patients with chronic diseases.

The widespread use of genetic engineering has made it possible to prepare analogues of natural occurring insulins by exchanging, deleting and adding one of more of the amino acid residues. For decades, insulin preparations with different duration of action have been developed and put on the market, including long-acting, medium-acting and fast-acting insulin preparations. Thus WO 2014 009316 A1 describes a medicament for the treatment of diabetes, which medicament comprises insulin derivatives having an extremely long duration of action. However, no particular dosage regimen has been proposed.
SUMMARY OF THE INVENTION

With a view to improved patient compliance and patient safety we have now developed a therapy based on a new mode of administration. The invention provides an improved drug treatment regimen for the treatment of subjects suffering from diabetes mellitus, and in particular from diabetes mellitus type 2.

Accordingly, in one embodiment, the invention provides a method for the treatment, prevention or alleviation of diabetes mellitus in a subject in need of such treatment, which method comprises administering to this subject a dosage of a long-acting insulin analogue, at intervals less frequent than once-daily, a single dose of a long-acting insulin analogue, which method comprises the steps of

(A) a titration phase, during which phase the subject is administered at suitable administration intervals with an individual, incremental start-up titration dosage, using a single dose or multiple dose dispenser, until the desired steady-state is reached; which titration phase is optionally followed by

(B) a maintenance phase, during which phase the subject is administered with sequential individual maintenance (single) dosages at suitable administration intervals, that are less frequent than once-daily.

In another embodiment the invention provides a long-acting insulin analogue for use in the treatment of diabetes mellitus, wherein the substance is administered at intervals less frequent than once-daily.

In a third embodiment the invention provides a long-acting insulin analogue for the manufacture of a medicament for use in the treatment of diabetes mellitus, wherein the medicament is prepared to be administered at intervals less frequent than once-daily.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

DETAILED DISCLOSURE OF THE INVENTION

Novel dosage regimen and methods of treatment

In one aspect the invention provides a method for the treatment, prevention or alleviation of diabetes mellitus in a subject in need of such treatment, which method comprises administering to this subject a dosage of a long-acting insulin analogue according to a particular dosage regimen described in more details below.
In another aspect the invention relates to a long-acting insulin analogue for use in the treatment of diabetes mellitus, wherein the substance is administered by a particular dosage regimen, as described below.

In a third aspect the invention relates to the use of a long-acting insulin analogue for the manufacture of a medicament for use in the treatment of diabetes mellitus, wherein the medicament is prepared to be administered according to a particular dosage regimen, as described below.

Advantages of the method of administration according to the present invention include:

- A simple and convenient concept;
- Safe administration, no "double dosing";
- Easy to instruct;
- No wastage;
- Minimized risk of needle clogging;
- Use of existing device, compact cartridge; and
- Flexible w.r.t. required titration steps; etc.

**Long-acting insulin analogues**

In one aspect, the method of therapy according to the present invention comprises administration of a long-acting insulin analogue.

As defined herein, the term "long acting insulin analogue" means that the insulin analogue for use according to the invention, when applied to the subject in question, is capable of reaching a steady state that allows for a sufficient glycemic control (e.g. keeps blood sugar levels at a steady and stable level) following administration of a less frequent than daily dosage of the long-acting insulin analogue.

The insulin analogue for use according to the invention may be any long-acting insulin analogue intended for the treatment, prevention or alleviation of diabetes mellitus. Preferred long-acting insulin analogues for use according to the invention include the analogues described in e.g. WO 2014 009316 A1, and may in particular be selected from the following:

- A14E, B16H, B25H, B29K(N^2-eicosadieioy]-YGlul-[2-(2-[2-(2-aminoethoxy)-ethoxy]acetylamino]ethoxy]ethoxy][acetyl], desB30 human insulin (Compound 1);
- A14E, B16H, B25H, B29K(N^6-hexadecandieioy]-YGlul), desB30 human insulin (Compound 2);
- A14E, B16H, B25H, B29K(N^2-eicosanediioy]-YGlul), desB30 human insulin (Compound 3);
A14E, B25H, desB27, B29K(N\(^{-}\)-(octadecandioyl-YGlu), desB30 human insulin (Compound 4);
A14E, B25H, desB27, B29K(\(^{-}\)-octadecanediol-yGlu-OEG-OEG), desB30 human insulin (Compound 5); and

In a particular embodiment the insulin analogue for use according to the invention is
A14E, B16H, B25H, B29K(N\(^{-}\)-eicosanedioyl-YGlu-[2-(2-{2-(2-aminoethoxy)ethoxy}acetyl-amino)ethoxy]ethoxy]acetyl), desB30 human insulin (Compound 1); further characterised by the following structure:

![Chemical structure image]

**Method of administration (dosage regimen)**

The method of administration according to the present invention aims at reaching a steady state that allows for a beneficial glycaemic control (i.e. keeps blood sugar levels at a steady and stable level) in the subject in question for a sufficient period of time, which time period is prolonged when compared to conventional therapy.

The method of administration according to the invention involves administration of a single dosage of a long-acting insulin analogue at intervals less frequent than once-daily (i.e. at intervals longer than 24 hours), during a period of time of at least 3 months, at least 6 months, or of at least 1 year.

In one embodiment the method comprises administration of a single dose to the subject with a frequency in the range of from every 2\(^{nd}\) day to every 11\(^{th}\) day, on average.

In another embodiment the method comprises administration of a single dose to the subject with a frequency in the range of from every 3\(^{rd}\) day to every 10\(^{th}\) day, on average.
In a third embodiment the method comprises administration of a single dose to the subject with a frequency in the range of from every 4th day to every 9th day, on average.

In a fourth embodiment the method comprises administration of a single dose to the subject with a frequency in the range of from every 5th day to every 8th day, on average.

In a fifth embodiment the method comprises administration of a single dose to the subject with a frequency in the range of from every 6th day to every 7th day, on average.

In a sixth embodiment the method comprises administration of a single dose to the subject once a week, i.e. on every 7th day, on average, during a period of time of at least 3 months, at least 6 months, or of at least 1 year.

Monitoring of the administration and target values

In order to secure maintenance of satisfactory glycemic levels, the method of administration according to the invention may be monitored by conventional techniques, which include determination of the fasting blood glucose level, and/or determination of the hemoglobin HbA1C level. Such determinations should be carried out on a regular basis, e.g. before meals (fasting blood glucose), after administration of the long-acting insulin analogue, or after intake of the largest meal of the day.

The target blood glucose level currently considered as a goal for patients with type 2 diabetes is 4-7 mmol/L before meals (i.e. fasting blood glucose), and 5-10 mmol/L when measured two hours after meals (or even 5-8 mmol/L if the glalculated hemoglobin target is not met); and a glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, Hb1c, or HbA1c) value of ≤ 7%; taking into consideration the age of the patient in question, the prognosis, the level of glycemic control, the duration of diabetes, the presence of diabetes complications or comorbidities, and the risk for and ability to perceive hypoglycemia, and similar factors to be considered by the competent medical doctor.

Preferably the fasting blood/plasma glucose measurement is taken at the same time on each day of measurement. In one embodiment the fasting blood/glucose measurement is taken at least 8 hours after eating. In another embodiment the fasting blood/glucose measurement is taken before breakfast.

Therapeutic stages

While the method of administration according to the present invention aims at reaching a glycemic steady state, following single shot administration of a long-acting insulin analogue, for a sufficient period of time which is less frequent than once daily, the method of administration according to the invention may be regarded as composed of two basic phases, i.e.

A) a titration (introduction or start-up) phase; and
B) a maintenance (steady state) phase.

During the titration phase, the subject is administered at suitable intervals (of from every 2nd to every 7th day) with an individual, start-up titration dosage, e.g. in increments of about 35 IU/interval, using a single dose or multiple dose dispenser, until a desired steady-state is reached.

In one embodiment, the titration phase involves the use of a multiple dose dispenser (pen or syringe), until steady state has been reached.

As one example, the titration phase may be based on the use of a multiple dose dispenser (pen or syringe) holding a 100 international units (U100) formulation, e.g. a compact cartridge of 1.5 ml, which provides for four-five fixed dosages of e.g. 35 international units (equivalent to 4x5 IU of a U100 formulation), during which titration phase the subject is titrated with about 35 units/week (corresponding to about 5 units/day) for four-five weeks (4-5 titration steps), until a steady state has been reached.

In another embodiment, the titration phase involves the use of a single shot dispenser (i.e. a fixed dose device), until steady state has been reached.

As another example, the titration phase may be based on the use of a single shot disposable device holding a 100 international units (U100) formulation, which provides for titration with a titration dosage of e.g.

35 units/week (equivalent to 5 units/day) using a "35 units/week disposable pen or syringe" per titration step; or
70 units/week (equivalent to 10 units/day), using a "70 units/week disposable pen or syringe" per titration step;
210 units/week (equivalent to 30 units/day), using a "210 units/week disposable pen or syringe" per titration step;
350 units/week (equivalent to 50 units/day), using a "350 units/week disposable pen or syringe" per titration step;
490 units/week (equivalent to 70 units/day), using a "490 units/week disposable pen or syringe" per titration step;
630 units/week (equivalent to 90 units/day), using a "630 units/week disposable pen or syringe" per titration step;

for four-five weeks (4-5 titration steps), until a steady state has been reached.

A therapeutic steady state is usually reached following four-five titration steps of a long-acting insulin analogue, but should be monitored as described above.

When the target values have been reached, the maintenance phase can start.

During the maintenance phase, the subject is administered with sequential individual (single dose) maintenance dosage at suitable administration intervals.
As an example, the maintenance phase may be based on the use of a single shot disposable device holding a 100 international units (U100) formulation, which provides for administration with a maintenance dosage of e.g.

35 units/week (equivalent to 5 units/day) using a "35 units/week disposable pen or syringe" per maintenance step; or
70 units/week (equivalent to 10 units/day), using a "70 units/week disposable pen or syringe" per maintenance step;
210 units/week (equivalent to 30 units/day), using a "210 units/week disposable pen or syringe" per maintenance step;
350 units/week (equivalent to 50 units/day), using a "350 units/week disposable pen or syringe" per maintenance step;
490 units/week (equivalent to 70 units/day), using a "490 units/week disposable pen or syringe" per maintenance step; or
630 units/week (equivalent to 90 units/day), using a "630 units/week disposable pen or syringe" per maintenance step.

In case an alternative dosage is needed, supplemental administration may be accomplished by use of a combination of two (or more) of these fixed dosage devises. As one example a dosage of 280 units/week (equivalent to 40 units/day) may be composed using two different dose-unit injections, a 70 units/week and a 210 units/week (10+30).

Other maintenance dosages may be administered in a similar fashion using alternative dosage combinations.

**Target population**

The method of administration according to this invention has been developed with a view to improve convenience and to increase compliance of the therapy in patients suffering from diabetes.

In one embodiment, the method of administration according to this invention is applied to patients suffering from diabetes mellitus type 2.

In another embodiment, the method of administration according to this invention is applied to diabetic (type 2) patients that are currently treated with oral anti-diabetic drugs, and which patients are not well controlled with respect to achieving glycemic control.

In a third embodiment, the method of administration according to this invention is applied to diabetic (type 2) patients that are currently on once-daily (long-acting) basal insulin therapy.

In a fourth embodiment, the method of administration according to this invention is applied to diabetic (type 2) patients that are currently in a basal bolus insulin therapy. A basal-bolus therapy involves taking a longer acting form of insulin to keep blood glucose
levels stable through periods of fasting, and separate injections of shorter acting insulin to prevent rises in blood glucose levels resulting from meals.

In a fifth embodiment, the method of administration according to this invention is applied to diabetic (type 2) patients that are currently in a GLP-1 therapy, i.e. a therapy based on administration of glucagon-like peptide-1 (GLP-1) analogues.

**Kits of parts**

For convenience, and in order to improve compliance, the long-acting insulin analogue for use according to the method of administration of the invention is provided in the form of a "kit-of-parts". The kit-of-parts of the invention comprises a container/dispenser for use with a needle, which container/dispenser comprises the long-acting insulin analogue for use according to the method, and instructions for use.

In one embodiment the kit-of-parts for use during the titration phase of the invention comprises

A) a single shot dosing device, comprising a selected dosage of a long-acting insulin analogue, and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

B) one or more prefilled disposable single-shot devices, each comprising a selected dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

C) instructions for use.

In another embodiment the kit-of-parts for use during the titration phase of the invention comprises

A) a multiple dosing device, comprising a selected dosage of a long-acting insulin analogue, and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

B) one or more prefilled disposable single-shot devices, each comprising a selected dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

C) instructions for use.

In another embodiment the kit-of-parts for use during the maintenance phase of the invention comprises

A) one or more prefilled disposable single-shot devices, each comprising a selected dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

B) instructions for use.
In a third embodiment the kit-of-parts of the invention comprises a compact cartridge providing for one or more fixed dosages, co-packed with the same number of safety needles, for one-time use.

In a fourth embodiment the kit-of-parts of the invention comprises a compact cartridge of e.g. 1.5 ml, holding e.g. a 100 international units (U100) formulation, providing for one or more fixed dosages of e.g. 35 international units, co-packed with the same number of safety needles, for one-time use.

In a fifth embodiment the kit-of-parts of the invention comprises a compact cartridge of 1.5 ml, holding a 100 international units (U100) formulation, providing for four fixed dosages of 35 international units, co-packed with four safety needles, for one-time use.

In further embodiments the kit-of-parts of the invention comprises one or more prefilled disposable single-shot devices comprising a long-acting insulin analogue in a dosage of 35 units, and/or 70 units, and/or 210 units, and/or 350 units, and/or 490 units, and/or 630 units per device.

In an even further embodiment the invention provides a packaged pharmaceutical preparation comprising a long-acting insulin analogue and instructions for administering the insulin according to a less frequent than once-daily dosing regimen, as described above.

Definitions

International units

In pharmacology an international unit (IU) is a unit of measurement for the amount of a particular substance, and the mass or volume that constitutes one international unit varies based on the substance in question. For the purpose of easier comparison across substances the variance is based on a biological activity or effect. International units are typically used to quantify e.g. vitamins, hormones, vaccines, blood products, and similar biologically active substances including insulins.

In respect of insulins, 1 IU is defined as the mass or volume of compound which is biologically equivalent to 0.0347 mg of human insulin (of 28.8 IU/mg).

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated by reference to the accompanying drawing (Fig. 1), which shows a graphic presentation of principle underlying the method of administration (dosage regimen) according to this invention, including the use of a single or multiple dose titration dispenser (for the titration phase), and a single dose maintenance dispenser (for the maintenance phase).
1. A method for the treatment, prevention or alleviation of diabetes mellitus in a subject in need of such treatment, which method comprises administering to this subject a dosage of a long-acting insulin analogue, at intervals less frequent than once-daily, a single dose of a long-acting insulin analogue, which method comprises the steps of

(A) An titration phase, during which phase the subject is administered at suitable administration intervals with an individual, incremental start-up titration dosage, using a single dose or multiple dose dispenser, until the desired steady-state is reached; optionally followed by

(B) A maintenance phase, during which phase the subject is administered with sequential individual maintenance (single) dosage at suitable administration intervals.

2. The method according to claim 1, wherein said diabetes mellitus is diabetes mellitus type 2.

3. The method according to either one of claims 1-2, wherein the long-acting insulin analogue is administered to the subject with a frequency in the range of from every 2\textsuperscript{nd} day to every 11\textsuperscript{th} day, on average.

4. The method according to any one of claims 1-3, wherein the long-acting insulin analogue is administered to the subject once a week, on average.

5. The method according to any one of claim 1-4, wherein the long-acting insulin analogue is selected from the group consisting of

A14E, B16H, B25H, B29K(\textsuperscript{N}eicosanedioyl-YGIu-[2-(2-[2-(2-aminoethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl), desB30 human insulin (Compound 1);

A14E, B16H, B25H, B29K(\textsuperscript{N}hexadecandioyl-YGIu), desB30 human insulin (Compound 2);

A14E, B16H, B25H, B29K(\textsuperscript{N}eicosanedioyl-YGIu), desB30 human insulin (Compound 3);

A14E, B25H, desB27, B29K(\textsuperscript{N}octadecandiyo-YGIu), desB30 human insulin (Compound 4);

A14E, B25H, desB27, B29K(\textsuperscript{f}octadecanediyo-yGlu-OEG-OEG), desB30 human insulin (Compound 5); and

6. The method according to any one of claim 1-4, wherein the long-acting insulin analogue is A14E, B16H, B25H, B29K(N'-eicosanediyl-yGlu-[2-(2-{2-(2-aminoethoxy)- ethoxy}acetylamino)ethoxy]ethoxy)acetyl), desB30 human insulin (Compound 1).

7. A long-acting insulin analogue for use in the treatment of diabetes mellitus, wherein the substance is administered at intervals less frequent than once-daily, which treatment comprises the steps of

(A) An titration phase, during which phase the subject is administered at suitable administration intervals with an individual, incremental start-up titration dosage, using a single dose or multiple dose dispenser, until the desired steady-state is reached; optionally followed by

(B) A maintenance phase, during which phase the subject is administered with sequential individual maintenance (single) dosage at suitable administration intervals.

8. The use of a long-acting insulin analogue for the manufacture of a medicament for use in the treatment of diabetes mellitus, wherein the medicament is prepared to be administered at intervals less frequent than once-daily, which treatment comprises the steps of

(A) An titration phase, during which phase the subject is administered at suitable administration intervals with an individual, incremental start-up titration dosage, using a single dose or multiple dose dispenser, until the desired steady-state is reached; optionally followed by

(B) A maintenance phase, during which phase the subject is administered with sequential individual maintenance (single) dosage at suitable administration intervals.

9. A kit of parts for use during the titration phase comprising

A) a single shot dosing device, comprising a selected dosage of a long-acting insulin analogue, and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

B) one or more prefilled disposable single-shot devices, each comprising a selected dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and

C) instructions for use.
10. A kit of parts for use during the titration phase comprising
   A) a multiple dosing device, comprising a selected dosage of a long-acting insulin
   analogue, and one or more auxiliary agents (adjuvants, excipients, carriers and/or diluents); and
   B) one or more prefilled disposable single-shot devices, each comprising a selected
   dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants,
   excipients, carriers and/or diluents); and
   C) instructions for use.

11. A kit of parts for use during the maintenance phase comprising
   A) one or more prefilled disposable single-shot devices, each comprising a selected
   dosage of a long-acting insulin analogue and one or more auxiliary agents (adjuvants,
   excipients, carriers and/or diluents); and
   B) instructions for use.

12. The kit of parts according to any one of claims 9-11, wherein the prefilled
    disposable single-shot device comprising a long-acting insulin analogue in a dosage of 35
    units, and/or 70 units, and/or 210 units, and/or 350 units, and/or 490 units, and/or 630 units
    per device.

13. A packaged pharmaceutical preparation comprising a long-acting insulin
    analogue and instructions for administering the insulin according to a less frequent than
    once-daily dosing regimen.
Fig. 1

OW

Single shot - maintenance dosages

Covers 80% of T2 diabetes patients

- 630 units/week
- 490 units/week
- 350 units/week
- 210 units/week
- 70 units/week

90 units/day

70 units/day

50 units/day

30 units/day

10 units/day

Insulin Pen
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) and/or both national classification and IPC.

B. FIELDS SEARCHED

Minimal documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimal documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Document member of the same patent family

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Authorized officer:
Schnack, Anne
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