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Datasheet for the decision of 14 November 2023

Case Number: T 1047/21 - 3.3.07

Application Number: 14714692.2

Publication Number: 2983697

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Language of the proceedings: EN

Title of invention:
TREATMENT OF DIABETES MELLITUS BY LONG ACTING FORMULATIONS OF INSULINS

Patent Proprietor:
SANOFI

Opponent:
Cooke, Richard

Headword:
Treatment of Diabetes with long acting insulins / SANOFI

Relevant legal provisions:
RPBA 2020 Art. 12(4)
EPC Art. 54, 56

Keyword:

Late-filed evidence - admitted (yes)
Novelty - main request (yes)
Inventive step - main request (no), auxiliary requests 1-5 and 7-8 (no)

Decisions cited:

G 0003/89, G 0011/91, G 0002/10, G 0001/16, G 0002/08

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1047/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 November 2023

Appellant: (Patent Proprietor)	SANOFI 46 avenue de la Grande Armée 75017 Paris (FR)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Respondent: (Opponent)	Cooke, Richard Elkington and Fife LLP Patents Department 3-4 Holborn Circus London EC1N 2HA (GB)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 April 2021 revoking European patent No. 2983697 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

I. European patent EP 2983697 (hereinafter "the patent") was granted on the basis of 11 claims. The sole independent claim of the patent as granted read as follows:

"1. 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 300 U/mL [equimolar to 300 IU human insulin] of insulin glargine."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step and it was not sufficiently disclosed.

III. The opposition division took the decision to revoke the patent. The decision was based on the patent as granted as main request and 17 auxiliary requests.

IV. The decision of the opposition division, posted on 15 April 2021, cited *inter alia* the following documents:

D1: WO 2011/144673
D5: Owens *et al.*, Diabetes Technol. Ther., 2008, 10(5), 333-349
D6: Mathieu *et al.*, J. Clin. Endocrinol. Metab., March 2013, 98(3), 1154-1162

D7: Meneghini *et al.*, Diabetes Care, 2013, 36, 858-864
D8: Joslin Clinic, Joslin Diabetes Center, 2012, Policies and Procedures, 1-3
D12: Fran Cogen, https://www.healthcentral.com/article/traveling-with-diabetes, 14 April 2009
D13: Chandran and Edelman, Clinical Diabetes, 2003, 21(2), 82-85
D14: Metha and Wolfsdorf, Endocrinology and Metabolism Clinics of North America, September 2010, 39(3), 573-593

V. The opposition division decided in particular that the main request and auxiliary requests 1 to 17 were not novel over D1.

VI. The patent proprietor (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its statement setting out the grounds of appeal the appellant defended its case on the basis of a main request and 8 auxiliary requests filed therewith, which had all been filed as auxiliary requests during the first instance proceedings.

With the letter dated 9 November 2023, the main request was withdrawn and auxiliary request 1 was made to the new main request. The following auxiliary requests 2 to 8 were maintained without renumbering.

During oral proceedings auxiliary request 6 was renumbered as auxiliary request 1. The remaining auxiliary requests were maintained without renumbering.

The following table gives an overview of the correspondence of the requests on file with those of the first instance proceedings:

Current request	Request as filed with the statement of grounds of appeal	Request as numbered during oral proceedings in the opposition proceedings	Request as initially filed in the opposition proceedings
MR	AR1	AR1	AR4 (04.01.21)
AR1	AR6	AR2	AR10a (03.03.21)
AR2	AR2	AR6	AR5 (04.01.21)
AR3	AR3	AR9	AR7 (04.01.21)
AR4	AR4	AR10	AR7a (03.03.21)
AR5	AR5	AR15	AR10 (04.01.23)
AR7	AR7	AR16	AR11 (04.01.21)
AR8	AR8	AR17	AR11a (03.03.21)

VIII. The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 1 of the main request read as follows:

"1. 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 25 h to 28 h or in the range of 20 h to 23 h on at least two days

per week, and wherein the average time interval from the previous administration is about 24 h as calculated on a weekly basis, said formulation comprising 300 U/ml [equimolar to 300 IU human insulin] of insulin glargine."

Claim 1 of auxiliary request 1 corresponded to claim 1 of the main request wherein the following feature was added after "for use in the treatment of Type I or Type II Diabetes Mellitus":
"and a reduction in the risk of nocturnal hypoglycemia compared with a treatment with Lantus U100 insulin glargine".

Claim 1 of auxiliary request 2 corresponded to claim 1 of the main request wherein the time interval from the previous administration on at least two days per week was specified "as calculated on a weekly basis".

Claim 1 of auxiliary request 3 read as follows:

"1. An aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus and a reduction in the risk of nocturnal hypoglycemia, wherein the formulation is administered once daily to a patient, and 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 on at least two days per week, and wherein the average time interval from the previous administration is about 24 h, said formulation comprising 300 U/ml [equimolar to 300 IU human insulin] of insulin glargine."

Claim 1 of auxiliary request 4 corresponded to claim 1 of auxiliary request 3 wherein the following feature

was added after "a reduction in the risk of nocturnal hypoglycemia":
"compared with a treatment with Lantus U100 insulin glargine".

Claim 1 of auxiliary request 5 corresponded to claim 1 of auxiliary request 3 wherein the average time interval from the previous administration was specified "as calculated on a weekly basis".

Claim 1 of auxiliary request 7 corresponded to claim 1 of auxiliary request 3 wherein also the time interval from the previous administration on at least two days per week was specified "as calculated on a weekly basis".

Claim 1 of auxiliary request 8 corresponded to claim 1 of auxiliary request 7 wherein the following feature was added after "a reduction in the risk of nocturnal hypoglycemia":
"compared with a treatment with Lantus U100 insulin glargine".

IX. Oral proceedings were held before the Board on 14 November 2023.

X. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of a main request corresponding to auxiliary request 1 filed with the statement setting out the grounds of appeal. Alternatively the appellant requested that the patent be maintained on the basis of one of auxiliary requests 1 to 5 and 7 to 8 corresponding to the auxiliary requests 2-8 filed with the statement setting out the grounds of appeal wherein present auxiliary request 1 was filed as auxiliary request 6.

XI. The respondent requested that the appeal be dismissed.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The main request fulfilled the requirements of Article 54 EPC. D1 did not implicitly disclose the administration regimen defined in claim 1 of the main request, in particular because further realistic alternatives to the alleged implicit dosage regimen could be conceived (see Case Law of the Boards of Appeal, I.C.4.3, 5th paragraph).

(b) The main request met the requirements of Article 56 EPC. The subject-matter of claim 1 of the main request differed from D1 in the definition of the administration regimen (frequency and extent of variation as well as average time interval). Two unexpected effects had been substantiated in the examples of the patent, namely maintained glycemic control and maintained hypoglycemic events (see examples 1, 3 and 6, in particular paragraphs [0107], [0256], [0265] and [0352]). The objective technical problem as formulated during oral proceedings resided thus in the provision of a more flexible dosage regimen that did not affect efficacy and safety. The skilled person would have expected reduced glycemic control when administration is differed and an increased risk of hypoglycemic events due to insulin stacking when administration is done before the end of duration of action of insulin glargine. None of the cited prior art documents provided a reasonable expectation of success to maintain glycemic control and hypoglycemic events while varying the

administration time of insulin to the extent claimed. The cited documents related indeed to different insulin analogs than the claimed insulin glargine U300. Moreover, even D6 and D7, which concerned the study of a flexible administration of insulin Degludec, would still recommend an administration at the same time every day. D6 would even substantiate a negative impact of a flexible administration regimen on FPG (see Figure 1 of D6). Furthermore D8, D12 and D13 related to exceptional circumstances and actually suggested that regular variation of the administration time impacted glycemic control.

(c) Auxiliary request 1 complied with Article 56 EPC. The reduction in risk of nocturnal hypoglycemia compared with a treatment with Lantus U100 insulin glargine constituted a further distinguishing feature over D1. The objective technical problem resided thus in the provision of a flexible dosage regimen for the reduction of the risk of hypoglycaemia at night. The skilled person would not have expected a reduction of nocturnal hypoglycemia with a flexible administration regimen due to insulin accumulation. This was also not suggested in any of the cited prior art documents. In particular D1 mentioned only hypogylcemic events in general and not specifically nocturnal hypoglycemia.

(d) Auxiliary requests 2 to 5 and 7 to 8 involved an inventive step for the same reasons as for the main and first auxiliary requests.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The main request did not meet the requirements of Article 54 EPC. The "once daily" administration of insulin glargine U300 disclosed in D1 implicitly anticipated the administration regimen defined in claim 1 of the main request. In light of common general knowledge as illustrated by D14, "once daily" in D1 meant an administration at approximately the same time every day, wherein the variability included at least a +/- 2 hours time window. Moreover the specific deviation on at least 2 days per week was merely a non-novel selection within the dosage regimen of D1. In particular, no technical effect required to confer novelty to a dosage regimen according to G 2/08 had been substantiated.

(b) The main request did not comply with Article 56 EPC. The subject-matter of claim 1 of the main request differed from D1 in the definition of the administration regimen (frequency of variation and average time interval). No particular effect was linked thereto. In particular there was no prejudice in the prior art against small deviations from a strict 24 hours administration. The objective technical problem resided thus in the provision of an alternative administration regimen of an aqueous pharmaceutical formulation comprising 300 U/ml of insulin glargine for use in the treatment of Type I or Type II Diabetes Mellitus. The skilled person would have been aware from common general knowledge (as revealed by D8, D12, D13 or D14) and D6 or D7 that long acting insulin analogs having a flat PK/PD profile and a long duration of action such as insulin glargine U300 could be administered following a flexible

administration regimen. The claimed administration regimen constituted thus an arbitrary selection from D1.

(c) Auxiliary request 1 did not fulfill the requirements of Article 56 EPC. The reduction of incidence of hypoglycaemia was disclosed in general in D1 (see page 10 line 30 to page 11 line 2 and claim 23). Furthermore D1 specified that a flatter basal insulin profile minimized the tendency to hypoglycemia. Since D1 also stated that insulin glargine U300 had a flatter profile than Lantus U100 insulin glargine, D1 already suggested that insulin glargine U300 would lead to a reduction of the risk of hypoglycemia, including nocturnal one, compared to Lantus U100 insulin glargine. This additional distinguishing feature could thus not provide inventiveness.

(d) Auxiliary requests 2 to 5 and 7 to 8 did not involve an inventive step for at least the same reasons as for the main and first auxiliary requests.

Reasons for the Decision

Main request

1. Novelty

1.1 The appellant contested the decision of the opposition division that claim 1 of the present main request (corresponding to auxiliary request 1 in the opposition proceedings) lacked novelty over D1.

1.2 It was undisputed among the parties that D1 discloses an aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus (see *e.g.* page 10 lines 4-5) wherein the formulation contains preferably 300 U/ml of insulin glargine (see *e.g.* page 10 lines 6-8) and the formulation is preferably administered "once daily" (see page 10 line 15). D1 discloses therefore the same formulation for use in the treatment of the same disease as present claim 1. The administration regimen of D1, *i.e.* "once daily", is however not further described in D1.

1.3 The issue under dispute was the interpretation of the term "once daily" in D1 and whether D1 implicitly discloses an administration regimen according to present claim 1.

Standard to be applied in the present case

1.4 Having regard to the administration regimen, D1 does not disclose any well-defined range. The extensive discussion in the impugned decision regarding the issue of a novel selection from a broader range is therefore not appropriate in the present case.

1.5 Rather the "gold standard" as developed in the context of Article 123(2) EPC (see Case Law of the Boards of Appeal, 10th edition 2022, II.E.1.3.1, G 3/89, G 11/91 G 2/10 and G 1/16) and which has become the standard approach in terms of disclosure applying not only to the assessment of added subject-mater but also of validity of a claimed priority and novelty (see *e.g.* G 1/16 item 17) should be applied to assess the actual disclosure of D1. When applying this standard to the assessment of the disclosure of a prior art document, disclosed is what a skilled person would derive

directly and unambiguously from the entire document, using common general knowledge, and seen objectively and relative to the effective date of the document.

Disclosure of D1 - "once daily"

1.6 The appellant considered that "once daily" in D1 should be given its literal meaning *i.e.* "once a day at any time of the day". No other interpretation based on documents relating to other insulin analogs could be applied to present insulin glargine U300. In any case, D1 would not specifically disclose the present administration regimen, at least not the claimed frequency of variation.

1.7 The respondent considered "once daily" in D1 as meaning an administration at approximately the same time every day, wherein the variability includes at least a +/- 2 hours time window, as revealed by D14(see page 579, last sentence of penultimate paragraph). D1 would consequently implicitly disclose the variable administration regimen of present claim 1.

1.8 The Board considers that the administration regimen of D1 has to be interpreted in a reasonable manner, *i.e.* taking into account the medical use to which it applies and in light of common general knowledge. A literal interpretation of the term "once daily" disconnected from the medical use to which it refers would not correspond to what the skilled person would directly and unambiguously derive from D1. The Board observes that it appears to have been part of common general knowledge at the filing date of D1, that in view of their mode of action long-acting insulin analogs for use in the treatment of Diabetes Mellitus were not to be administered at "any time of the day" but at "around

the same time every day" (see in particular D14, page 579 to 582, and D5, e.g. page 336, 1st column, 2 first paragraphs).

1.9 While it is to be expected that in practice some variability in the administration will occur since patient compliance will not be 100%, the Board agrees with the appellant that novelty is not a question of probability. Similarly the issue of whether occasional departure from a strict 24 hours administration in case of *e.g.* travelling across time zones would be acceptable or not and the possibility of tying up the administration to a daily event, is also not relevant when determining whether D1 actually directly and unambiguously discloses a variable administration regimen.

1.10 It remains to be determined whether the "once daily" administration regimen mentioned in D1 directly and unambiguously discloses an administration regimen falling under the one defined in claim 1, namely:

- the following extent of variation and frequency: "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 on at least two days per week",

and

- the following average time interval: "from the previous administration is about 24 h as calculated on a weekly basis".

1.11 Concerning the extent of variation, D14 discloses that long-acting insulin analogs are to be administered at the same time of the day with a window of +/- 2 hours. The Board considers indeed that the last sentence of the first paragraph in the section "Long-Acting

Insulins" on page 579 of D14 refers, as the entire paragraph, to any long-acting insulin analogs and is not limited to Insulin detemir. D14 is an excerpt of a textbook and can thus be considered as representing common general knowledge at the filing date of D1. Since D1 discloses that Insulin glargine U300 is a long acting insulin analog (see, *e.g.* title of D1), it appears that the "once daily" dosage regimen of D1 would be understood by the skilled person as the administration of insulin glargine U300 every 24 hours +/- 2 hours. Thus D1 implicitly discloses an extent of variation overlapping with the one defined in present claim 1. There is however no disclosure thereof in combination with the present average time interval, *i.e.* about 24 h calculated on a weekly basis.

1.12 Regarding the frequency of variation, independently of the issue of the time basis for the calculation of the "at least two days per week", the specific variability claimed is not directly and unambiguously derivable from D1. The vaguely defined administration regimen in D1, which is considered to be interpreted as 24 hours +/- 2 hours, covers a broad number of different possible frequencies. While there might be some overlap with the presently claimed frequencies, there is no particular teaching thereof, let alone in combination with the claimed average time interval ("about 24 h as calculated on a weekly basis").

1.13 It follows that the claimed administration regimen is not directly and unambiguously derivable from D1.

1.14 As a result, the subject-matter of claim 1 of the main request is novel over D1.

2. Inventive step

2.1 In agreement with both parties, the Board considers D1 to represent the closest prior art. The disclosure of D1 has already been discussed in the context of novelty (see above 1.2 to 1.13).

2.2 The subject-matter of present claim 1 differs from the treatment disclosed in D1 in the nature of the administration regimen.

2.3 As shown in example 3, the claimed administration regimen had no negative impact on glycemic control (see data on HbA1c and FPG, *i.e.* Fasting Plasma Glucose) and hypoglycemia events (see in particular paragraphs [0256] to [0265]) compared to a modelled strict 24 hours administration regimen. Thus, as explained by the appellant, the claimed administration regimen achieves good safety and efficacy. Good efficacy and safety are also reported in D1 (see e.g. page 1 lines 20 to 21 together with page 4 lines 8 to 9 and page 10 line 30 to page 11 line 2).

2.4 Thus, starting from D1, the objective technical problem resides in the provision of an alternative administration regimen of an aqueous pharmaceutical formulation comprising 300 U/ml of insulin glargine for use in the treatment of Type I or Type II Diabetes Mellitus, *i.e.* with maintained efficacy and safety.

2.5 The Board considers that the solution offered in claim 1 of the main request does not involve an inventive step starting from D1 in combination with common general knowledge and D6 or D7 for the reasons detailed in items 2.5.1 to 2.5.6 below.

2.5.1 As brought forward by the respondent, occasional variability of insulin administration time is commonly considered as permissible, even in the case of fast acting insulin (see D8, page 1, 4th and 5th paragraphs; D12, page 2, 3rd paragraph and page 5, 1st paragraph; and D13, page 83, 2nd column, 3rd full paragraph). Moreover, as stated above under novelty (see 1.11), an administration of long-acting insulin at intervals of 24 hours +/- 2 hours appears to form part of common general knowledge and to apply to any long-acting insulin, thus including insulin glargine U300. Hence, the skilled person would have been aware from common general knowledge that intermittent variability from a strict 24 hours administration regimen by +/- 2 hours is acceptable, independently of the type of insulin administered especially for long acting insulin analogs. In this context, D14 does not mention any issue regarding hypoglycemic events or glycemic control, so that the skilled person would not have expected any negative impact thereupon.

2.5.2 Furthermore, D1 states that insulin glargine U300 has an even flatter PK/PD profile than the commercially available long-acting insulin, insulin glargine U100 (Lantus®), see *e.g.* page 4 lines 1-9 of D1. D1 also discloses a prolonged activity for insulin glargine U300 compared to insulin glargine U100 (see *e.g.* example 18). As argued by the respondent, these properties would be understood by the skilled person as allowing for an even greater variability in the administration time.

2.5.3 This relationship between longer duration of action as well as flatter PK/PD profile and greater variability of the administration time has been further confirmed in the case of insulin Degludec in D6 or D7. Indeed the

overall conclusion of the authors in these documents is that due to the ultra-long duration of action and low variability of insulin Degludec, its injection time may be varied from day to day without compromising efficacy and safety (see D6, page 1155, 2nd full paragraph and page 1161, 2nd full paragraph; D7, paragraph bridging pages 862 and 863).

While the findings of D6 and D7 indeed pertain to insulin Degludec, they nevertheless provide a more general teaching regarding the properties of insulin analogs having a very long duration of action and a flat PK/PD profile, independently of the mechanism responsible for these properties. In view of the disclosure in D1 of the same properties for insulin glargine U300, the skilled person would have understood without the exercise of any inventive skills that insulin glargine U300 would similarly allow for a greater variability of administration time without compromising efficacy and safety.

In this context and contrary to the appellant's opinion, the fact that insulin Degludec has a longer duration of action than insulin glargine U300 would not prevent the skilled person from drawing the above conclusion. Both insulin analogs are indeed described as providing a flat and stable action over at least 24 hours. In view of the lower half-life of insulin glargine U300 the skilled person would, if anything, have expected insulin stacking issues to be reduced compared with insulin Degludec.

2.5.4 The administration of insulin glargine U300 at a time interval from the previous administration of 22 hours to 26 hours, in particular at 23 or 25 hours, cannot therefore provide any inventiveness to the present

administration regimen, in particular since the weekly average time interval remains 24 hours.

2.5.5 Finally, as argued by the respondent, the claimed frequency of variation, *i.e.* "at least 2 days per week", appears to constitute an arbitrarily chosen feature, because no particular effect has been shown to be linked thereto. Since the weekly average time interval remains 24 hours, despite the apparent high variability of the claimed administration regimen, it remains within the framework of accepted variations around a strict 24 hours administration regimen already suggested in the prior art for ultra long acting insulin analogs having a flat PK/PD profile.

2.5.6 Maintained efficacy and safety would thus have been reasonably expected for an administration of insulin glargine U300 at a time interval from the previous administration of 22 hours to 26 hours on at least 2 days per week with a weekly average time interval from the previous administration being 24 hours.

2.6 The arguments provided by the appellant in support of an inventive step, which have not already been addressed by the above reasoning, are not convincing for the reasons detailed below in items 2.6.1 to 2.6.4.

2.6.1 The appellant brought forward that the skilled person would have expected insulin stacking to occur when administration is done before the end of duration of action of insulin glargine, *i.e.* around 24 hours, leading to increased risk of hypoglycemia, *i.e.* reduced safety. The fact that in theory some insulin stacking may occur is not disputed. The Board considers however that the appellant has not provided any evidence that the skilled person would have considered the level of

insulin glargine U300 at *e.g.* 22 hours after the last injection high enough to lead to an insulin stacking such that the risk of hypoglycaemia would significantly increase. Hence the skilled person would not have seen in this potential but limited insulin stacking any hindrance to a variability of administration time at least between 22 and 23 hours of the preceding administration (*i.e.* corresponding to the variation considered acceptable from common general knowledge).

2.6.2 The appellant argued that the skilled person would have expected reduced glycemic control in case of administration of insulin glargine U300 after the end of duration of action thereof. The Board notes that, as argued by the respondent, glycemic control is not solely achieved by the administration of basal insulin in the treatment of Diabetes Mellitus, be it type I or II, at least since combination therapies with bolus insulin or short-acting insulin analogs are used (see *e.g.* D14, page 582, 2nd and 3rd paragraphs under "insulin regimens"). Furthermore, the appellant has not provided any evidence that an administration between 25 and 26 hours after the last injection (*i.e.* corresponding to the variation considered acceptable from common general knowledge) would indeed have been considered by the skilled person as leading to a significant risk of reduced glycemic control.

In this context the appellant considered that D6 actually indicated to the skilled person that delaying long acting insulin injection might result in deterioration of glycemic control. The Board disagrees. The overall teaching of D6 is that injection time of an ultra long acting insulin with flat PK/PD profile may be varied from day to day without compromising efficacy and safety (see 2.5.3). Moreover the data referred to

by the appellant regarding Fasting Plasma Glucose levels in D6 for insulin Degludec fixed compared to flexible administration regimens (see Figure 1 page 1158) are not relevant in the present context. The flexible administration regimen defines indeed much higher variations of insulin administration time than the +/- 2 hours considered in the present argumentation (namely 8 to 40 hours, see page 1155, right column, 2nd paragraph under "procedures" of D6).

2.6.3 The Board finally observes that the isolated passages of D6 and D7 referred to by the appellant as recommending an administration at the same time every day (see D6 page 1160, left column, second paragraph and D7 page 862, right column, last paragraph) were cited out of their respective context and cannot put into question the overall conclusion and teaching of these documents.

2.6.4 It follows that, contrary to the appellant's view, the maintenance of a low number of hypoglycemic events and maintenance of glycemic control with an administration at 22 to 26 hours intervals compared to a fixed 24 hours dosage regimen would not have been considered as unexpected by the skilled person.

2.7 Accordingly, the subject-matter of claim 1 of the main request does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

3. Inventive step

3.1 The subject-matter of claim 1 of auxiliary request 1 differs from the one of claim 1 of the main request in

that the feature "and a reduction in the risk of nocturnal hypoglycemia compared with a treatment with Lantus U100 insulin glargine" was added to the medical use claimed.

3.2 D1 already discloses the reduction of incidence of hypoglycemia in the treatment of Type I and Type II Diabetes Mellitus by administering insulin glargine U300 (see page 10 line 30 to page 11 line 2). This passage concerns hypoglycemia as a whole and thus generally encompasses nocturnal hypoglycemia.

The same reasoning as developed for claim 1 of the main request applies *mutatis mutandis* to claim 1 of auxiliary request 1. It follows that maintained reduction of nocturnal hypoglycemia would have been expected for insulin glargine U300 administered according to the presently claimed variable administration regimen compared to insulin glargine U300 administered according to a 24 hours "strict" regimen.

3.3 Furthermore, the technical teaching of D1 is that insulin glargine U300 provided a flatter PK and PD profile than Lantus U100 insulin glargine, when considering a 24 hours "strict" administration regimen (see page 4 lines 4 to 5). D1 further indicates in general that a flatter profile minimizes the tendency to produce hypoglycemia (see page 3 lines 21 to 23). It follows that the skilled person would have learned from D1 that insulin glargine U300 led to reduced risk of hypoglycemia compared with Lantus U100 insulin glargine, when administered according to a 24 hours "strict" regimen.

Since the same level of safety is expected for insulin glargine U300 administered according to the present regimen or according to the regimen of D1, a reduced risk of nocturnal hypoglycemia would consequently be expected for insulin glargine U300 administered according to the present regimen compared to Lantus U100 insulin glargine.

3.4 Hence, the subject-matter of claim 1 of auxiliary request 1 does not fulfill the requirements of Article 56 EPC.

Auxiliary requests 2 to 5 and 7 to 8

4. Inventive step

4.1 Auxiliary requests 3, 4 and 5 do not contain any feature not already discussed in the context of the main request and auxiliary request 1.

4.2 Claims 1 of auxiliary requests 2, 7 and 8 differ from the one of main request or of auxiliary request 1 respectively in that the frequency of the variation, *i.e.* "at least two days per week", is further specified as "calculated on a weekly basis". No particular effect directly linked to this feature has been brought forward. Furthermore, in the context of the main request, the frequency of administration has been considered to amount to an arbitrary chosen feature independently of any time period for its calculation (see 2.5.5).

4.3 The subject-matter of claim 1 of auxiliary requests 2 to 5 and 7 to 8 does thus not involve any inventive step for at least the reasons developed for the main and/or first auxiliary requests.

4.4 As a result, none of the auxiliary requests 2 to 5 and 7 to 8 meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated