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**Long-acting insulin
analogues in the
treatment of diabetes
mellitus type 1¹**

Executive Summary

¹ Translation of the executive summary of the final report “Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 1” (Version 1.0; Status: 18.02.2010). Please note that this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Long-acting insulin analogues in the treatment of diabetes mellitus type 1

Executive summary

Background

On 22 February 2005 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) in writing to assess the benefit of long-acting insulin analogues (LAIAs) in the treatment of diabetes mellitus type 1. Details of the commission were specified beforehand with the G-BA on 2 February 2005 on the basis of a draft commission.

Research question

The aims of this research were:

- to assess the benefit of long-term treatment with an LAIA compared with treatment with a longer-acting insulin based on human insulin

and

- to assess the benefit of LAIAs compared with each other,

in each case in patients with diabetes mellitus type 1. The focus of the assessment was on patient-relevant outcomes.

Methods

The methods of this assessment were described in advance in the report plan. The report plan, version 1.0 of 16 October 2005, was published on the Internet on 23 October 2005. Subsequently, amendment 1 to the report plan was published on 22 June 2007. Comments could be submitted up until 26 July 2007 on version 1.0 of the report plan and on amendment 1. Unclear aspects of these written comments were discussed on 30 August 2007 in a scientific debate with the authors of the comments. The comments and the documentation of the debate have been published on the Internet in a separate document (“Documentation and appraisal of comments submitted on the report plan”). As a result of the commenting procedure, a revised report plan (version 2.0 of 21 January 2008) was published. The preliminary assessment, the preliminary report, was published on 7 July 2009 on the Internet. Comments could be submitted on this preliminary report up until 6 August 2009. Unclear aspects arising from the comments were then discussed with the authors of the comments in a scientific debate on 22 September 2009 to determine their relevance for the final report. The preliminary report also underwent an external review. Following the scientific debate, IQWiG produced this final report. The comments submitted on the preliminary report and the minutes

of the scientific debate are presented in a separate document entitled “Documentation and appraisal of the hearing on the preliminary report”.

The benefit assessment was performed on the basis of randomized controlled trials (RCTs). For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE and CENTRAL. The period up to July 2009 was covered. In addition, literature indexes of relevant secondary publications (systematic reviews, HTA reports) and publicly accessible clinical trial registries and drug approval documents were screened. Moreover, the manufacturers of LAIAs were asked to provide further information.

RCTs lasting at least 24 weeks were included in which insulin detemir or insulin glargine was compared with a longer-acting insulin based on human insulin or the 2 LAIAs were compared with each other. The literature screening was undertaken by 2 reviewers independently of each other. After an assessment of study quality, the results of the individual studies were collated according to therapy goals and outcomes. Adults were assessed separately from children and adolescents, both for the drugs investigated and the therapy regimens applied (particularly time and frequency of administration of longer-acting insulin).

Results – studies with adults

Search results

A total of 12 relevant studies were identified for which sufficient transparent information was available, and which were therefore included in the benefit assessment.

The 12 relevant studies were assigned to the individual research questions as follows:

- In 10 studies, treatment with a long-acting insulin analogue was compared with human insulin, 6 of which used insulin glargine and 4 of which used insulin detemir. A total of 3511 adults were randomized to treatment groups.
- Insulin detemir was compared with insulin glargine in 2 studies. In these studies a total of 769 adults were randomized to treatment groups.

Out of the 12 relevant studies, 11 were manufacturer-sponsored. Unpublished clinical study reports (CSRs) on these studies were provided by the manufacturers and were included in the assessment. 2 studies were unpublished (1430 and 1582), so that their assessment was based solely on the CSRs.

Design and quality of the relevant studies

All 12 studies were open label and investigated the use of LAIAs in a once-daily (insulin glargine) or once- or twice-daily (insulin detemir) subcutaneous injection regimen. In some

cases the studies differed greatly in the therapy regimen used (e.g. once- or twice-daily dose of basal insulin). Within the drug classes the assessment was therefore differentiated according to therapy regimen. It was noticeable in the comparative studies with human insulin that in several studies it was not possible to optimize the administration of neutral protamine Hagedorn (NPH) insulin (i.e. adapt to the individual situation), as designated in the approval. Thus, the results of these studies were not transferable to the treatment situation in Germany.

The maximum treatment period was 2 years (applying to one study comparing insulin detemir with NPH insulin; the treatment period of the remaining studies was between 24 and 54 weeks). No study was identified that aimed to assess effects of long-term treatment on late complications of diabetes mellitus.

As all studies were open label due to the difficulty in blinding patients and treating staff, it would have been advisable at least to introduce blinding for the assessment of outcomes or for dose titration. This was usually not done. For this reason, 9 of the 12 studies were assessed as having “minor deficits”. The lack of blinding led to a high risk of bias for subjective outcomes in all studies. Furthermore, 2 studies comparing insulin glargine vs. NPH insulin and one study comparing insulin detemir vs. NPH insulin were assessed as having “major deficits” due to unclear allocation concealment (4019, 1582) and/or inadequate application of the ITT² principle (3101, 4019, 1582). In these studies there was a high risk of bias for all outcomes.

Late complications and mortality

On the basis of the studies included, no conclusions could be drawn concerning the long-term effects on the risk of diabetes-related late complications.

As none of the studies were designed to investigate mortality, deaths recorded in the safety evaluation were drawn on to analyse the outcome “all-cause mortality”. In the comparison of insulin detemir vs. NPH insulin, only one study (1595) had a numerically noticeably higher number of deaths under insulin detemir. This effect was not observed in the other 3 studies on insulin detemir.

Changes in the ocular fundus

With regard to changes occurring in the ocular fundus as recorded within the framework of the safety evaluation, no noticeable differences between the treatment groups were shown in any therapy regimen.

Overall, there was no proof of an advantage of insulin analogues regarding the outcomes “mortality” and “diabetes-related late complications”.

² Intention To Treat

Inpatient hospital treatment for any cause

Due to a lack of data, there was no proof of an advantage of either of the insulin analogues regarding the necessity of inpatient hospital treatment.

Serious hyperglycaemia

From the available data, it was not possible to derive proof of an advantage of any treatment option regarding the prevention of serious hyperglycaemia.

Hypoglycaemia in conjunction with long-term blood glucose lowering

The data on the HbA1c value and severe/serious hypoglycaemia were presented in a sufficiently transparent manner in all studies. Due to the close relationship between hypoglycaemia and the HbA1c value, conclusions concerning the benefit of an agent were drawn only on the basis of a conjoint assessment of both components of this outcome.

Although hypoglycaemia was measured in all studies, they were all susceptible to systematic bias due to the consistently open label design, including the lack of or unclear blinding when measuring outcomes. Under these conditions, only the data on severe and serious hypoglycaemia as reported were seen as providing sufficient certainty of results. Regarding non-severe hypoglycaemia, only those cases that were defined by a combination of hypoglycaemia-associated symptoms and a confirmed blood glucose measurement were seen as relevant to the conclusion, as only these were viewed as providing sufficient measurement certainty. As these confirmed, non-severe cases of hypoglycaemia were also associated with a high risk of bias, only those results showing a sufficiently large difference between the treatment groups were viewed as sufficient to provide proof of additional benefit. Based on empirical evidence, a value of 0.75 was set as the upper limit of the 95% confidence interval for the odds ratio. If the individual confidence interval was fully below this limit, then the probability was considered to be very low that the effect could be solely due to systematic bias. However, this planned procedure was not applied, as no statistically significant differences were found for the corresponding outcomes.

Insulin glargine vs. NPH insulin

There was no proof of an advantage of insulin glargine over NPH insulin in any of the investigated therapy regimens when blood glucose lowering and severe (nocturnal) or non-severe (nocturnal) hypoglycaemia were assessed conjointly.

Insulin detemir vs. NPH insulin

In the comparisons of insulin detemir vs. NPH insulin with either once-daily administration or once- to twice-daily administration in each group from the start of the study, no proof of an

advantage of insulin detemir over NPH insulin was shown when blood glucose lowering and severe (nocturnal) or non-severe (nocturnal) hypoglycaemia were assessed conjointly.

In the comparison of insulin detemir vs. NPH insulin, each once (at start of study) or twice daily (during the study if necessary), there was an indication of a difference in favour of insulin detemir when blood glucose lowering and severe nocturnal hypoglycaemia were assessed conjointly. However, when interpreting the results, it should be noted that they cannot be transferred to the German treatment situation due to the application modalities of basal insulin. There was no such indication for non-severe (nocturnal) hypoglycaemia.

Insulin detemir vs. insulin glargine

In the comparison of insulin detemir twice daily vs. insulin glargine once daily, when considering blood glucose lowering and severe (nocturnal) or non-severe (nocturnal) hypoglycaemia conjointly, there was no proof of an advantage of either of the two insulin analogues.

Health-related quality of life

Utilizable data were available on the effect of LAIAs on health-related quality of life in 3 studies comparing insulin glargine vs. NPH insulin (3001, 3004, 3101). These studies evaluated a sub-field of health-related quality of life, well-being, using the W-BQ22 or W-BQ12³. The results from Study 4019 could not be utilized.

Overall, the data provided no proof of an advantage of insulin analogues regarding health-related quality of life.

Treatment satisfaction

Six studies assessed treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQc⁴ or DTSQs⁵). The comparison of insulin glargine vs. NPH insulin was the subject of 4 studies; one study compared insulin detemir vs. NPH insulin and another study insulin detemir vs. insulin glargine. A further study comparing insulin detemir vs. insulin glargine used the Insulin Treatment Satisfaction Questionnaire (ITSQ).

Insulin glargine vs. NPH insulin

The results from the two studies 3001 and 3004 comparing insulin glargine (evening) vs. NPH insulin (once or twice daily) were heterogeneous. There was no statistically significant difference in Study 3004, whereas a statistically significant difference in favour of insulin

³ Well-being Questionnaire

⁴ Diabetes Treatment Satisfaction Questionnaire change version

⁵ Diabetes Treatment Satisfaction Questionnaire original status version

glargine was present in Study 3001. However, even when considering the statistically significant Study 3001 alone, the effect was not large enough to assume a relevant difference in favour of insulin glargine. Overall, there was no proof of an advantage of insulin glargine over NPH insulin regarding treatment satisfaction.

Study 4010 comparing insulin glargine vs. NPH insulin, each administered once daily in the evening, showed a statistically significant and relevant effect in favour of insulin glargine. However, this was not confirmed by Study 3101. Due to the high risk of bias, the results of both studies were classified as uncertain. Overall, the data provided no proof of an advantage of insulin glargine over NPH insulin regarding treatment satisfaction.

There was no proof of superiority or inferiority of treatment with insulin glargine compared to treatment with NPH insulin in any of the above-mentioned therapy regimens for the DTSQ dimensions of perceived hyper- and hypoglycaemia.

Insulin detemir vs. NPH insulin

Study 1582 on insulin detemir vs. NPH insulin (each once or twice daily) showed neither superiority nor inferiority of either of the two therapy options with regard to treatment satisfaction, as measured by the DTSQs. The same applied to the DTSQ dimensions of perceived hyper- and hypoglycaemia.

Insulin detemir vs. insulin glargine

Treatment satisfaction was evaluated in Study 1372 on insulin detemir vs. insulin glargine using the DTSQs. Although a statistically significant difference was shown in favour of insulin detemir, the relevance of the effect could not be estimated due to a lack of data. The assessment of treatment satisfaction with the ITSQ in Study 1430 showed no statistically significant difference between the treatment groups.

Overall, there was no proof of an advantage of insulin detemir over insulin glargine regarding treatment satisfaction.

Other adverse events

None of the studies investigated the long-term safety of insulin analogues. In order to estimate the risk of harm, results on the following individual outcomes were used: serious adverse events, therapy discontinuations due to adverse events, and injection site reactions. In addition, weight change throughout the duration of the study was assessed.

Insulin glargine vs. NPH insulin

There was no proof of an advantage or disadvantage of insulin glargine compared to NPH insulin regarding serious adverse events.

Moreover, there was no proof of an advantage or disadvantage of insulin glargine compared to NPH insulin regarding therapy discontinuations due to adverse events or injection site reactions.

The meta-analytical summary of data on weight showed no proof of a difference between insulin glargine and NPH insulin regarding changes in body weight or body mass index (BMI).

Insulin detemir vs. NPH insulin

There was no proof of an advantage or disadvantage of insulin detemir compared to NPH insulin regarding serious adverse events. The same applied to therapy discontinuations due to adverse events.

The data showed an indication of a disadvantage of insulin detemir compared to NPH insulin regarding injection site reactions.

Concerning weight change, there was proof of less weight gain with insulin detemir compared to NPH insulin. The meta-analysis of all studies showed a mean difference of approx. 0.7 kg. The clinical relevance of this difference remained unclear.

Insulin detemir vs. insulin glargine

Overall, there was no proof of an advantage or disadvantage of insulin detemir compared to insulin glargine regarding the complex “adverse events including injection site reactions”. Moreover, there was no proof of a difference in weight change between the two therapy options.

Subgroup analyses

Results on different subgroups were reported for 2 studies comparing insulin glargine vs. NPH insulin (Studies 3001 and 3004). For the comparison of insulin detemir vs. NPH insulin, there were only subgroup results available from Study 1335 and qualitative results from Study 1476. Study 1372 comparing insulin detemir vs. insulin glargine also reported results on subgroup analyses.

The subgroup analyses on sex and age that were carried out for the HbA1c and hypoglycaemia outcomes were particularly relevant for this report. There were no indications in any of the comparisons that the results according to sex or age differ from the overall result (p -value for interaction > 0.2 in each case).

Results – studies with children and adolescents

Search results

A total of 5 relevant studies were identified for which sufficient transparent information was available and which were therefore included in the benefit assessment.

In all 5 studies, treatment with a long-acting insulin analogue was compared with treatment with human insulin, 2 of which used insulin glargine, and 3 of which used insulin detemir. A total of 1300 children and adolescents were randomized to treatment groups.

All 5 relevant studies were manufacturer-sponsored and unpublished CSRs on all studies were provided by the manufacturers and included in the assessment. 2 out of 3 studies on insulin detemir were unpublished (1604 and 1689), so that their assessment was based solely on the CSRs.

Design and quality of the relevant studies

All 5 studies were open label and investigated the use of LAIAs administered by means of once- or twice-daily subcutaneous injection. In some cases the studies differed greatly in the therapy regimen used (e.g. once- or twice-daily administration of basal insulin). Thus, the assessment was also differentiated according to therapy regimen within the comparison of insulin glargine vs. NPH insulin (2 out of 5 studies). It was noticeable in the glargine studies that it was not consistently possible to optimize the administration of NPH insulin (i.e. adapt to the individual situation), as designated in the approval. Thus, the results were barely transferable to the treatment situation in Germany.

The maximum treatment duration in the studies with children and adolescents was 52 weeks (one study on insulin detemir). The other studies with children and adolescents lasted between 24 weeks and 28 weeks.

As all studies were open label due to the difficulty in blinding patients and treating staff, it would have been advisable to introduce blinding for the assessment of outcomes or for dose titration. This was usually not done. The lack of blinding led to a high risk of bias in subjective outcomes for all studies. Moreover, both studies comparing insulin glargine vs. NPH insulin (3003, 4030) were assessed as having “major deficits” due to inadequate application of the ITT principle, so that there was generally a high risk of bias in their results.

Late complications and mortality

On the basis of the studies included, no conclusions could be drawn concerning the long-term effects on the risk for diabetes-related late complications.

As none of the studies were designed to investigate mortality, deaths recorded in the safety evaluation were drawn on to analyse the outcome “all-cause mortality”. There were no deaths in the studies with children and adolescents.

Changes in the ocular fundus

There was no proof of an advantage of any of the treatment options investigated regarding changes in the ocular fundus or vision. Overall, the data were inadequate.

Overall, there was no proof of an advantage of insulin analogues regarding the outcomes “mortality” and “diabetes-related late complications”.

Inpatient hospital treatment for any cause

Due to a lack of data, there was no proof of superiority of the effect of LAIAs over NPH insulin regarding the necessity of inpatient hospital treatment.

Serious hyperglycaemia

Overall, few hyperglycaemic events were noted during the safety evaluation. The data did not provide proof of an advantage of one of the treatment options regarding serious hyperglycaemia.

Hypoglycaemia in conjunction with long-term blood glucose lowering

The data on the HbA1c value and severe/serious hypoglycaemia were presented in a sufficiently transparent manner in all studies. Due to the close relationship between hypoglycaemia and the HbA1c value, conclusions concerning the benefit of an agent were drawn only on the basis of a conjoint assessment of both outcomes. The assessment was carried out in the same way as for adults.

Insulin glargine vs. NPH insulin

In the comparison of insulin glargine vs. NPH insulin, there were no noticeable differences in severe hypoglycaemia (total, nocturnal) or non-severe hypoglycaemia (total, nocturnal) in the presence of similar long-term blood glucose lowering. Overall, when assessed conjointly, there was no proof of an advantage of either of the two therapy options.

Insulin detemir vs. NPH insulin

In the comparison of insulin detemir vs. NPH insulin, there were no noticeable differences in severe hypoglycaemia (total, nocturnal) or non-severe hypoglycaemia (total, nocturnal) in the presence of similar long-term blood glucose lowering. Thus, there was no proof of an advantage of either of the two therapy options.

Health-related quality of life

The effect of LAIAs on health-related quality of life was only investigated in one study (4030) comparing insulin glargine vs. NPH insulin in children and adolescents, which used the Diabetes Quality of Life Questionnaire for Youth (DQOLY).

Insulin glargine vs. NPH insulin

A statistically significant difference between the treatment groups was shown for the dimension “disease impact”, to the disadvantage of insulin glargine compared to NPH insulin. As the 95% confidence interval was not fully above the relevance limit of 0.2, the relevance of this effect could not be estimated with certainty. Furthermore, the effect on this patient-reported outcome was not sufficiently large that it could not be explained solely by the open label design. There was no statistically significant difference between the treatment groups for the other DQOLY dimensions. Overall, there was no proof of an advantage of NPH insulin over insulin glargine.

Treatment satisfaction

None of the included studies evaluated treatment satisfaction. Thus, there was no proof of advantage of insulin analogues over NPH insulin regarding this outcome.

Other adverse events

Overall, no study aiming to investigate long-term safety was identified. In order to estimate the risk of harm, results on the following individual outcomes were used: serious adverse events, therapy discontinuations due to adverse events, and injection site reactions. In addition, weight change throughout the duration of the study was assessed.

Insulin glargine vs. NPH insulin

With regard to serious adverse events, therapy discontinuations due to adverse events, and injection site reactions, there was no proof of superiority or inferiority of insulin glargine compared to NPH insulin in children and adolescents. Moreover, there was no proof of a difference in weight change between the two therapy options.

Insulin detemir vs. NPH insulin

With regard to serious adverse events, therapy discontinuations due to adverse events, and injection site reactions, there was no proof of greater risk of harm from either of the two therapy options. Under insulin detemir there was a smaller weight gain, on average approx. 0.4 kg/m² (based on BMI measurement). The relevance of this result is unclear.

Subgroup analyses

Study 3003 comparing insulin glargine vs. NPH insulin and Study 1689 comparing insulin detemir vs. NPH insulin reported results on subgroups that were relevant to the report. Neither of the two studies permitted the conclusion that there was a relevant difference in the effects according to the different age groups or to sex.

Conclusions

In general, the long-term benefit and harm of LAIAs have not been sufficiently investigated. Only one of the relevant studies lasted 24 months, the others only lasted approx. 6 to 12 months. Moreover, a large number of the studies that compared insulin analogues with NPH insulin could only be utilized to a limited extent, as NPH insulin had not been used optimally.

Studies with adults

Insulin glargine vs. NPH insulin

There is no proof of additional benefit from insulin glargine compared to NPH insulin.

Insulin detemir vs. NPH insulin

There is no proof of additional benefit from insulin detemir compared to NPH insulin. In one of the studies there was an indication of a difference in favour of insulin detemir with regard to the occurrence of severe (nocturnal) hypoglycaemia. However, NPH insulin was not optimally used in this study, so that no additional benefit could be established for insulin detemir.

There is an indication of a greater harm from insulin detemir regarding injection site reactions. In addition, there is proof of a smaller weight gain under insulin detemir. The mean difference between the groups was on average approx. 0.7 kg after 6 to 24 months. The relevance of the difference is unclear.

Insulin detemir vs. insulin glargine

There is no proof of additional benefit from either of the insulin analogues compared to each other.

Studies with children and adolescents

Insulin glargine vs. NPH insulin

There is no proof of additional benefit from insulin glargine compared to NPH insulin.

Insulin detemir vs. NPH insulin

There is no proof of additional benefit from insulin detemir compared to NPH insulin.

There was a smaller weight gain under insulin detemir, on average approx. 0.4 kg/m² (based on BMI measurement). The relevance of the difference is unclear.

Insulin detemir vs. insulin glargine

No study evaluated insulin detemir vs. insulin glargine in children and adolescents. Thus, there is no proof of additional benefit from either of the insulin analogues compared to each other.

Keywords: insulin analogues, insulin glargine, insulin detemir, NPH insulin, diabetes mellitus type 1

The full report (in German) is available on <http://www.iqwig.de/index.557.html>