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Glinides in the treatment of diabetes mellitus type 2¹

Executive Summary

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Executive summary

In its letter of 22 February 2005, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of various oral antidiabetics approved in Germany in the treatment of diabetes mellitus type 2. This also includes a benefit assessment of glinides.

Research question

The aims of this research were the comparative benefit assessments of long-term treatment with:

- nateglinide or repaglinide in each case vs. placebo or no treatment,
- nateglinide or repaglinide in each case vs. another glucose-lowering drug or non-drug treatment, and
- nateglinide or repaglinide vs. each other

in each case in patients with diabetes mellitus type 2.

The focus of the assessment was on patient-relevant outcomes.

Methods

The assessment was performed on the basis of randomized controlled trials (RCTs) investigating the research questions outlined above. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE, CENTRAL, and BIOSIS. Alongside the search for relevant primary literature, the search for relevant secondary publications used the MEDLINE and EMBASE databases. In addition, a search was made in the following specialized databases: Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE); and Health Technology Assessment Database (HTA Database). The period up to January 2009 was covered. Moreover, clinical trial registries and publicly accessible drug approval documents were screened and the manufacturers of repaglinide (Novo Nordisk) and nateglinide (Novartis) were asked to provide relevant information on published and unpublished studies.

RCTs with a duration of at least 24 weeks were included in which at least 1 of the 2 glinides mentioned was investigated within the framework of the valid European drug approval (status: July 2008 [repaglinide] and July 2006 [nateglinide]). The literature screening was

undertaken by 2 reviewers independently of each other. After an assessment of bias potential, the results of the individual trials were organized according to therapy regimens and collated according to therapy goals and outcomes. IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet (www.iqwig.de) and interested parties were invited to submit comments (hearing).

Unclear aspects of these written comments were discussed in a scientific debate on 10 February 2009. The final report was subsequently produced, taking the comments submitted into consideration.

Results

A total of 8 studies for the assessment of repaglinide and 2 studies for the assessment of nateglinide were identified. None of these studies were aimed at investigating the long-term benefit of glinides.

Two of the included studies were placebo-controlled (one on repaglinide and one on nateglinide). The following therapy options were compared in the active-controlled studies:

- repaglinide vs. metformin (2 studies)
- repaglinide vs. sulfonylureas (5 studies)
- nateglinide + metformin vs. sulfonylureas + metformin (1 study)

The treatment duration in the studies was 24 weeks to 14 months. The report's conclusions are therefore based exclusively on results from studies of comparatively short duration. No comparative studies were identified for further therapy options.

Unreported outcomes

There were no relevant studies covering the majority of pre-defined outcomes. This applied particularly to the following outcomes: mortality, late complications, inpatient treatments, hyperosmolar and ketoacidotic comas, symptoms caused by chronic hyperglycaemia, health-related quality of life and patient satisfaction.

Most of the studies had included data on deaths and late complications within the framework of evaluating adverse events. However, due to the comparatively small number of patients and the short duration of the included studies, there were relatively few events. Due to insufficient data, the benefit (or harm) of glinides with regard to late complications and mortality is thus unclear.

Reported outcomes

Information was only available on hypoglycaemia in relation to glucose control, serious adverse events and other adverse events such as a change in body weight or body mass index (BMI), at least for some of the therapy comparisons. However, even for these outcomes, the reporting of results was mostly insufficient. This also applied to some extent to studies, where the clinical study report (CSR) had been provided by the study sponsor concerned.

Hypoglycaemia in relation to long-term glucose control

In all comparisons of treatment options, the data on the conjoint assessment of long-term glucose lowering and hypoglycaemia were insufficient.

With regard to severe and serious hypoglycaemia in conjunction with glucose lowering, the data did not provide proof of a difference in harm potential for the 2 glinides compared to their corresponding treatment options. However, the data were insufficient, as events were rare or non-existent in the studies.

With regard to non-severe, confirmed cases of hypoglycaemia in conjunction with glucose lowering, the evaluation of repaglinide compared with sulfonylureas remained unclear overall due to insufficient data. There was no proof of variation in the occurrence of non-severe confirmed cases of hypoglycaemia for the other treatment options investigated. However, apart from the comparison of repaglinide with metformin, there was only one study available for these evaluations.

Harm potential (serious adverse events and study discontinuations due to adverse events)

None of the relevant studies included the aim of investigating the long-term safety of glinides. Data on serious adverse events and study discontinuations due to adverse events were extracted from the identified studies for a general evaluation of the harm potential. Due to the size and duration of the studies, the results are only of limited value.

With reference to the occurrence of such events, the analysis of results on serious adverse events did not show any statistically significant differences between repaglinide or nateglinide and the therapy alternatives investigated.

With reference to study discontinuations due to adverse events, there was a statistically significant difference between the intervention and comparator groups in the placebo-controlled repaglinide study (065) and in the study comparing nateglinide with sulfonylureas (both in combination with metformin; Study 2308). In Study 065, there were statistically significantly fewer study discontinuations due to adverse events in the repaglinide group (low dose) than in the placebo group. However, according to information in the CSR, the discontinuations that occurred in the placebo group can be interpreted specifically as therapy failure. In Study 2308 on nateglinide, significantly more patients from the

gliclazide/metformin group discontinued the trial due to adverse events than from the nateglinide/metformin group. However, in view of the comparable number of patients with serious adverse events in both treatment groups, it cannot be deduced that there is less harm potential from nateglinide compared to sulfonylureas.

Overall, the results on serious adverse events and study discontinuations due to adverse events did not provide any indication of greater or lesser harm either for repaglinide or for nateglinide compared to one of the therapy options investigated.

Body weight and BMI

In both the placebo-controlled studies for repaglinide and nateglinide, there was a greater weight increase from taking the glinide than the placebo. This difference was statistically significant for nateglinide in a dose of 180 mg/day. The relevance of the effect of 1 kg is unclear. No test for statistical significance was performed in the repaglinide study.

In the 2 studies comparing repaglinide with metformin, only minimal weight changes occurred in the repaglinide group, while the patients receiving metformin lost on average 2 kg. The difference in weight was statistically significant in one of the studies; the other study contained no information on significance. Overall, there was an indication of greater weight loss from taking metformin. However, the relevance of the effect of 2 kg is unclear.

In the comparisons of both repaglinide (monotherapy) and nateglinide (combination therapy with metformin) with sulfonylureas, there was no statistically significant difference in any of the studies with regard to weight changes between the treatment groups. However, for nateglinide, this assessment was only based on one study.

Conclusions

Only short-term studies are available for both repaglinide and nateglinide. These studies provide no proof of benefit from glinides. Neither is there any proof of an additional benefit compared to other therapy options. However, the only comparative studies available are versus metformin or sulfonylureas. Compared to these therapy options, there is no proof of greater or lesser harm from glinides.

There was a complete absence of data in the studies on health-related quality of life and treatment satisfaction. With reference to weight change, there was an indication of greater weight reduction (2 kg) when taking metformin compared to repaglinide. The relevance of the effect is unclear.

There were no long-term studies available for either repaglinide or nateglinide that were designed to investigate microvascular or macrovascular late complications.

Overall, there is no proof of benefit or additional benefit from glinides.

Keywords: repaglinide, nateglinide, glinides, oral antidiabetics, diabetes mellitus type 2, systematic review

The full report (in German) is available on www.iqwig.de/index.650.html