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Evaluation of the therapeutic benefits and harms of exenatide¹

Executive Summary

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Background

In its letter of 17.11.2005, the Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) to produce a rapid report on the evaluation of the therapeutic benefits and harms of exenatide.

Research question

The aims of the planned review arose from the wording of the commission by the Federal Joint Committee, as well as from the approval status of exenatide for the treatment of patients with type 2 diabetes mellitus. The following questions were to be answered by the rapid report:

- In patients with type 2 diabetes mellitus receiving blood-glucose lowering treatment with metformin and/or sulfonylurea, is there a benefit of add-on exenatide versus add-on placebo or no add-on treatment?
- In patients with type 2 diabetes mellitus receiving blood-glucose lowering treatment with metformin and/or sulfonylurea, is there an additional benefit of add-on exenatide versus add-on active control?

The focus of the evaluation was on patient-relevant therapy goals.

Methods

The systematic literature search was performed in the databases MEDLINE (1966 to June 2007), EMBASE (1980 to June 2007), BIOSIS and CINAHL (July 2007), the Cochrane databases (July 2007), as well as in various databases of publishing companies. Furthermore, a search was performed in reference lists of relevant secondary publications (systematic reviews and HTA reports), study registries, and publicly accessible drug approval documents. In addition, the manufacturer of exenatide was asked to provide a list of studies.

The evaluation was based on randomised controlled trials (RCTs) that compared exenatide (as an add-on therapy to metformin and/or sulfonylurea in patients with inadequate blood glucose control despite receiving treatment with maximum tolerated doses of these oral antidiabetics) with add-on placebo or other add-on blood-glucose lowering therapies. The minimum study duration was 12 weeks.

The literature screening was performed by at least 2 reviewers independently of each other.

After an evaluation of study quality, the results of the individual studies were collated according to therapy goals and outcomes. If meaningful and feasible, meta-analyses of the data were performed.

Results

The literature search retrieved 5 studies for the evaluation of exenatide. Three placebo-controlled studies investigated blood-glucose lowering therapy with exenatide as add-on therapy to metformin and/or sulfonylurea. In 2 studies, exenatide was compared with insulin; in addition, all patients received metformin and sulfonylurea.

The following table provides an overview of the study outcomes investigated.

Table 1: Overview of patient-relevant outcomes for which data were available from the studies included^a

Study	HbA1c	Hypo-glycaemia	Adverse events	Weight	Health-related quality of life	Treatment satisfaction
Study number						
Publication						
2993-112						
DeFronzo 2005	•	•	•	•		
2993-113						
Buse 2004	•	•	•	•		
2993-115						
Kendall 2005	•	•	•	•		
H80-MC-GWAA						
Heine 2005	•	•	•	•	•	•
Secnik Boye 2006						
H80-MC-GWAD						
Nauck 2007	•	•	•	•	(•) ^b	(•) ^b

a: No data were available for the following outcomes: late complications, mortality, hyperosmolar and ketoacidotic coma, hyperglycaemia-related symptoms.

b: In the GWAD Study, data on health-related quality of life and treatment satisfaction were collected, but the results have not yet been published.

No relevant data were available in the studies included on the following outcomes: late complications of diabetes, mortality, hospital stays, hyperosmolar and ketoacidotic coma, or symptoms related to chronic hyperglycaemia.

Glycaemic control

Compared with placebo, exenatide showed a dose-dependent reduction in HbA1c. With a mean HbA1c baseline value of 8% to 9%, in the exenatide 5 µg group, HbA1c was reduced by a mean of 0.64% at Week 30; the reduction in HbA1c in the exenatide 10 µg group was 0.96 %.

In the active-controlled studies, the reduction in HbA1c was comparable between exenatide and insulin (about 1%); the non-inferiority of exenatide was demonstrated in both studies. In the GWAA Study, the proportion of patients with HbA1c ≤ 7% was similar in both treatment groups (exenatide 10 µg: 46%; insulin glargine: 48%). In the GWAD Study, the proportion was slightly higher with exenatide than with insulin (32% vs. 24%).

Severe hypoglycaemia

Severe hypoglycaemic episodes were reported in only 2 studies. No severe hypoglycaemic episodes were observed in the other studies. In the placebo-controlled Study No. 115, a severe hypoglycaemic episode was reported in one patient in the exenatide 5 µg group; no such episodes were reported in the other groups. In the active-controlled GWAA Study, 4 patients in each of the 2 treatment groups experienced severe hypoglycaemic episodes. The rate of patients with severe hypoglycaemic episodes was below 2% in both studies, and comparable between treatment groups. No difference was therefore shown between exenatide and placebo regarding the occurrence of severe hypoglycaemic episodes. This also applied to the comparison between exenatide and insulin glargine, as well as exenatide and biphasic insulin aspart.

Other adverse events

In the placebo-controlled studies, the adverse event rate and the rate of study discontinuations due to adverse events were higher with exenatide than with placebo. The rate of study discontinuations due to adverse events rose with the increase in dose of exenatide. In the meta-analysis, the difference to placebo was statistically significant for exenatide 10 µg. In contrast, serious adverse events were no more frequent with exenatide than with placebo.

Statistically significantly more adverse events and study discontinuations due to adverse events were reported with exenatide than with insulin glargine or insulin aspart. The serious adverse event rate was comparable between exenatide and insulin glargine or insulin aspart.

The most common adverse events with exenatide were gastrointestinal in nature. Nausea, vomiting, and diarrhoea were statistically significantly more common with both the 5 µg and 10 µg dose of exenatide than with placebo (results of the meta-analysis).

Nausea was the most common adverse event. If exenatide was administered in addition to metformin, which can also cause nausea, the risk difference to placebo was 17% for exenatide 5 µg and 26% for exenatide 10 µg. In Study No. 113, where exenatide was administered in addition to sulfonylurea, the risk difference was 32% for exenatide 5 µg and 44% for exenatide 10 µg. For vomiting, the risk difference to placebo was 9% (both exenatide doses); for diarrhoea, the risk difference was 5% (exenatide 5 µg) and 8% (exenatide 10 µg).

In the active-controlled studies, nausea, vomiting, and diarrhoea also occurred statistically significantly more frequently with exenatide than with insulin glargine or insulin aspart.

Weight

In all studies, patients receiving exenatide lost weight. Compared with placebo, the mean difference with exenatide 5 µg and exenatide 10 µg at Week 30 was -0.71 kg and -1.29 kg respectively (meta-analysis data). These differences were statistically significantly different compared with placebo.

In the active-controlled studies, in contrast to patients receiving exenatide, those receiving insulin gained weight. The mean difference between exenatide and insulin was -4.1 kg at Week 26 (insulin glargine) and -5.5 kg at Week 52 (insulin aspart). These differences in weight development were statistically significant.

Health-related quality of life

Data on health-related quality of life were collected in both active-controlled studies, but have so far only been reported for the GWAA Study. No differences in results were found between exenatide and insulin glargine regarding the assessment of patients' health status (rated with the EQ-5D) or vitality (rated with the vitality subscale of the SF-36). This also applied to the impact of treatment on flexibility regarding meals and activities of daily living, assessed with the Diabetes Treatment Flexibility Scale. The results may have been biased in favour of exenatide.

Treatment satisfaction

Treatment satisfaction was assessed in both active-controlled studies; however, data have been published only for the GWAA Study so far. In this study, treatment satisfaction increased in both the exenatide and insulin glargine group; this change was comparable between groups. Therefore, no advantage was shown for any treatment option. The results may have been biased in favour of exenatide.

Conclusion

The blood-glucose lowering effect of exenatide has been demonstrated. A superior effect of exenatide versus insulin on the lowering of blood glucose levels has not been demonstrated. Regarding the blood-glucose lowering effect, the studies available showed similar results for exenatide and insulin glargine or insulin aspart. Corresponding comparative data for other blood-glucose lowering therapies (e.g., oral antidiabetics) were not available.

A benefit or additional benefit of exenatide in respect of patient-relevant outcomes has not been demonstrated. In particular this refers to late complications of type 2 diabetes mellitus, but also to outcomes that can be measured in the short term, such as quality of life or treatment satisfaction.

A harmful effect of exenatide therapy regarding the occurrence of gastrointestinal adverse events has been demonstrated.

The impact of weight loss caused by exenatide is unclear. Indications of a simultaneous reduction in blood pressure exist; however, the benefit of this effect has not been demonstrated.

On the basis of the available data it remains unclear whether the exenatide-related reduction in blood-glucose levels or in weight leads to a long-term benefit or additional benefit regarding late complications of type 2 diabetes mellitus. The long-term harmful effects of exenatide therapy are also unclear. A long-term benefit or harm has therefore not been demonstrated, nor has the lack of a long-term benefit or harm.

Key words: incretin mimetics, GLP-1, exenatide, type 2 diabetes mellitus, systematic review