Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: a model of long-term clinical and cost outcomes


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study evaluated exenatide (10 microg twice daily) versus insulin glargine (once daily: 25 IU in the first year, and 40 IU subsequently) in patients with Type 2 diabetes in the UK who were inadequately controlled with combination oral antidiabetic agents (OADs).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
A cohort was generated for the model, based on the combined baseline demographics, complications and treatment groups of all patients in the randomised trial. The participants were predominantly Caucasian (82.3%) with a mean baseline age of 58.9 years and duration of diagnosed diabetes of 10 years. The criteria for study entry were inadequate glycaemic control, that is, glycosylated haemoglobin (HbA1c) level greater than 7.0% but no more than 10.0%, and treatment with metformin and sulfonylurea therapy (assumed to continue at the pre-study dose throughout the simulation).

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The main clinical trial was reported in 2005. Other effectiveness data from a 2-year open-label extension study, used for the sensitivity analysis, were presented in abstract form and were also reported in 2005. The economic model was published in 2004 and was based on several long-term data sources (e.g. the UK Prospective Diabetes Study, UKPDS, which contained data collected over more than 20 years). Resource use was not reported separately, but annual event costs were referenced to literature published between 1998 and 2003. The unit costs were taken from 2004 or inflated to 2004 values. The utility data were taken from studies published between 2002 and 2006.

Source of effectiveness data
The main treatment effects used to inform the already validated model were:

- the change in HbA1c,
- the change in systolic blood pressure,
the change in total cholesterol,
the change in low-density lipoprotein,
the change in high-density lipoprotein,
the change in triglycerides,
the change in body mass index,
the proportion with nausea, and
the hypoglycaemia rates per 100 patient-years.

For detail of the other clinical data used in the model, the reader should refer to Palmer et al. (see ‘Other Publications of Related Interest’ below for bibliographic details).

Modelling
The authors used the published and validated CORE Diabetes Model (Palmer et al, 2004, see ‘Other Publications of Related Interest’ below for bibliographic details), a computer simulation model comprising 15 interdependent Markov sub-models, to project the long-term clinical and cost-effectiveness outcomes expected with exenatide. A brief overview of the model was given but further details were published elsewhere. A lifetime horizon (35 years) was employed.

Sources searched to identify primary studies
The main baseline treatment effect data were derived from a published randomised controlled trial (Heine et al.). The authors also used data from a 2-year open-label extension study to provide data for use in the sensitivity analyses. The data sources used to inform the initial published model were not reported.

Methods used to judge relevance and validity, and for extracting data
The authors’ aim was to extrapolate the findings from the clinical trial (Heine et al.). The process by which this study, along with the study used to inform the sensitivity analysis, was identified and selected was not reported. Although, it was reported that it was a recent, relevant randomised controlled trial, it was unclear whether a review of the literature had been undertaken or if there were any additional trials available to the authors.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). Life expectancy was also reported. The health state utilities were derived from the UKPDS, two other publications (including one from Australia), a standard-gamble study conducted in the UK and a time trade-off study derived from the EQ-5D index (the latter two studies were used for disutility of weight gain and nausea). The benefits were discounted at a rate of 3.5% per annum.

Direct costs
Direct medical costs to the NHS were included in the analysis. These included study and concomitant medications, adverse events such as hypoglycaemia and ketoacidosis, screening and treatment for diabetic complications (e.g. myocardial infarction, stroke, retinopathy, kidney transplant, amputation etc.). The resource use data were drawn from the literature. Event costs from 2004 were reported. These were drawn from published national statistics and literature, or inflated to 2004 levels using an appropriate health care price index. The costs of exenatide, the drug not being approved or available in the UK at the time, were modelled on various proportionate assumptions relating to the US wholesale costs; the base case was 100%. Discounting was conducted at a rate of 3.5% per annum.
Statistical analysis of costs
The costs and quantities were treated deterministically.

Indirect Costs
Productivity costs were not relevant to the perspective of the study.

Currency
UK pounds sterling (£).

Sensitivity analysis
Sensitivity analyses were performed on key parameters. Specifically, the time horizon, discount rate, insulin dose, size and sustainability of HbA1c effect, (dis)utility value for weight loss (gain) and nausea. The impact of including test strip costs for the monitoring of blood glucose levels was also examined. The model examined sustainability via the impact of a 2-year delay in HbA1c progression (hypothetical, drawing on results seen in an animal study). The ranges used were drawn from the clinical trial and other published literature. The analysis was performed using a non-parametric bootstrapping approach, in which the progression of diabetes was modelled in 1,000 patients 1,000 times (second-order Monte Carlo simulation) to calculate the mean and standard deviation (SD) of life expectancy, quality-adjusted life expectancy and costs. The authors did not state what types of sensitivity analyses were performed.

Estimated benefits used in the economic analysis
The mean discounted life expectancy was improved by 0.057 (SD=0.213) years with exenatide. Life expectancy was 10.66 (SD=0.16) years with exenatide versus 10.61 (SD=0.15) years with insulin glargine.

The mean discounted quality-adjusted life expectancy was improved by 0.442 (SD=0.146) QALYs with exenatide. Quality-adjusted life expectancy was 7.39 (SD=0.11) QALYs) with exenatide versus 6.95 (SD=0.10) QALYs with insulin glargine.

Side effects were considered in the analysis. The difference in QALYs was mainly driven by changes in body weight and associated utility weights.

Cost results
The total mean costs were 29,401 (SD=676) in the exenatide arm compared with 19,489 (636) in the insulin glargine arm.

The mean incremental costs were 9,912 (SD=891).

Synthesis of costs and benefits
The incremental cost per QALY ratio was 22,420 per QALY gained.

From the sensitivity analysis, it was found that exenatide became dominant over insulin glargine at a price below approximately 27% of the US price.

The mean incremental costs and incremental outcomes from 1,000 simulations were plotted on a cost-effectiveness plane and used to generate cost-effectiveness acceptability curves. At a willingness-to-pay level of 30,000, there was an 80% probability that exenatide was cost-effective.

Other sensitivity analyses demonstrated that the incremental cost-effectiveness ratio was most sensitive to the disutility values applied for weight gain and nausea. Changes in HbA1c, body weight, long-term HbA1c stabilisation, daily dose of insulin, time horizon and discount rates had little impact on relative results.
Authors' conclusions
The use of exenatide is associated with improvements in life expectancy, quality-adjusted life expectancy and cumulative incidence of diabetes-related cardiovascular complications. It represents good value for money in the UK setting.

CRD COMMENTARY - Selection of comparators
The authors chose insulin glargine as the comparator since it represented a more advanced long-acting example of exogenous insulin therapy, the primary alternative therapy for this patient population. You should decide whether it represents the most appropriate comparator in your own setting.

Validity of estimate of measure of effectiveness
The estimates of effectiveness were primarily drawn from a single 26-week trial. It was not possible to assess the quality of this trial from the limited data provided here. The authors acknowledged that other large clinical trials for exenatide existed, but that data from these trials were not incorporated into the present analysis. They did not report the use of any systematic review of the literature when populating the model. The authors included some assumptions in the model about treatment-related complications (weight gain and nausea) for all time periods beyond the first 6 months in the model, favouring exenatide in both cases. It was unclear whether this was entirely consistent with the evidence from the clinical trial, which showed that exenatide was associated with a non-significant benefit in body mass index changes and a significant worsening of nausea incidence.

Validity of estimate of measure of benefit
The utilities were well reported and were taken from published studies. However, given that the positive results of the model were acknowledged to be driven (as to be expected, given that there were non-significant differences in HbA1c changes) by the (dis)utilities of assumed differences in side effects, favouring exenatide, it was not clear that these differences were supported by the clinical evidence.

Validity of estimate of costs
All the relevant categories of costs to the NHS perspective were included. Some relevant costs appear to have been excluded, such as the costs of HbA1c monitoring (applied in a sensitivity analysis) and primary care visits, although these were not likely to have affected the cost conclusions. The resource quantities and costs were taken from published sources and national statistics and were adequately reported as annual event costs. The prices were inflated appropriately to a single price year (2004). Appropriate discounting was applied. The costs and effectiveness were evaluated in bootstrapped simulations, thus allowing appropriate uncertainty handling.

Other issues
The authors compared the key input parameters with those from other studies, but did not compare them with other cost-effectiveness analyses. The authors noted that the study did not capture the effects of higher withdrawal rates from exenatide in the study (19.4% versus 9.7%), but anticipated that this would be unlikely to change the results of the study. The authors acknowledged some other potential limitations. For example, the simplified insulin titration schedule used in the key trial, which might have contributed to lower than normal insulin doses at the end of the study, and the lack of availability of the UK price for exenatide. Generalisability was not addressed. The results were not presented selectively, but caution is recommended when interpreting the results (for the reasons given under the commentaries for effectiveness and benefit measures).

Implications of the study
The aim of the report was to provide a timely and realistic indication of the cost-effectiveness of exenatide in the UK and the appropriateness of its prescription in the future. Therefore, the authors' conclusions indicate that, by their assessment, exenatide should be prescribed to UK NHS patients who are insufficiently controlled on OADs. The authors recommend that the analysis is repeated when the price of exenatide in the UK is known.
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Other publications of related interest
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Blood Glucose /analysis; Cost of Illness; Cost-Benefit Analysis; Diabetes Complications /epidemiology /prevention & control; Diabetes Mellitus, Type 2 /diagnosis /drug therapy /economics; Dose-Response Relationship, Drug; Drug Administration Schedule; Evaluation Studies as Topic; Female; Great Britain; Humans; Hypoglycemic Agents /economics /therapeutic use; Insulin /analogs & derivatives /economics /therapeutic use; Insulin Glargine; Insulin, Long-Acting; Male; Markov Chains; Middle Aged; Models, Economic; Peptides /economics /therapeutic use; Prognosis; Quality-Adjusted Life Years; Risk Assessment; Sensitivity and Specificity; Severity of Illness Index; Time Factors; Treatment Outcome; Venoms /economics /therapeutic use

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