

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final appraisal determination

### Liraglutide for the treatment of type 2 diabetes mellitus

This guidance was developed using the single technology appraisal (STA) process.

## 1 Guidance

- 1.1 Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate ( $\text{HbA1c} \geq 7.5\%$ , or other higher level agreed with the individual), and the person has:
- a body mass index (BMI)  $\geq 35 \text{ kg/m}^2$  in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, **or**
  - a BMI  $< 35 \text{ kg/m}^2$ , and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
- 1.2 Treatment with liraglutide 1.2 mg daily in a triple therapy regimen should only be continued as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been

shown (defined as a reduction of at least 1 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

- 1.3 Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:
- the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin **or** a sulphonylurea is contraindicated, **and**
  - the person is intolerant of thiazolidinediones **and** dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.
- 1.4 Treatment with liraglutide 1.2 mg daily in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c at 6 months).
- 1.5 Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.
- 1.6 People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in section 1.1 or 1.3, or who are receiving liraglutide 1.8 mg, should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.

## 2 The technology

- 2.1 Liraglutide (Victoza, Novo Nordisk) is a stable analogue of the natural hormone glucagon-like peptide-1 (GLP-1). GLP-1 acts by stimulating insulin secretion, suppressing glucagon secretion (a hormone that opposes the effects of insulin), inhibiting gastric emptying, and by reducing appetite and food intake. GLP-1 may also preserve or increase the number of insulin-secreting cells in the pancreas, although this has only been demonstrated in animal models and the duration of effect is unknown. Liraglutide is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea, or in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.
- 2.2 The most frequently reported adverse effects of liraglutide are gastrointestinal, including nausea, diarrhoea, vomiting, constipation, abdominal pain, and dyspepsia. These gastrointestinal adverse effects may occur more frequently at the start of treatment with liraglutide, and usually diminish within a few days or weeks on continued treatment. Hypoglycaemia may also be common, and is more common when liraglutide is used in combination with a sulphonylurea. Major hypoglycaemia has primarily been observed when combined with a sulphonylurea. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Liraglutide is administered once daily by subcutaneous injection. The recommended starting dosage is liraglutide 0.6 mg daily. After at least 1 week, the dose should be increased to 1.2 mg. The

summary of product characteristics also states that based on clinical response, after at least 1 week the dose can be increased to 1.8 mg. Liraglutide is available in a prefilled, disposable pen device comprising a pen injector and cartridge. Each pen holds 30 doses of 0.6 mg, 15 doses of 1.2 mg, or 10 doses of 1.8 mg. It is available in two pack sizes: 2 x 3 ml prefilled pens (£78.48), and 3 x 3 ml prefilled pens (£117.72) (excluding VAT, 'British national formulary' [BNF] edition 59). The drug costs for liraglutide as reported by the manufacturer are £2.62 and £3.92 per day (1.2 mg dose and 1.8 mg dose respectively), and £954.84 and £1432.26 per year (1.2 mg dose and 1.8 mg dose respectively). Costs may vary in different settings because of negotiated procurement discounts.

### **3 The manufacturer's submission**

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of liraglutide, and reviews of this submission by the Evidence Review Group and the Decision Support Unit (ERG and DSU; appendix B).

- 3.1 Six randomised controlled trials (RCTs) were identified and presented in the manufacturer's submission: LEAD-1, LEAD-2, LEAD-4, LEAD-5, LEAD-6 and the 1860 trial. The trials provided data for liraglutide in 4260 people with type 2 diabetes, all within its licensed indication. All six studies reported change in glycated haemoglobin (haemoglobin A1c or HbA1c) as the primary efficacy endpoint and lasted 26 weeks (three had open-label extensions). All studies conducted intention-to-treat analyses for the primary outcome. The following secondary outcomes were included in each study: percentage of patients reaching HbA1c of less than 7.0%, percentage of patients reaching HbA1c of less than 6.5%, mean weight change from baseline, mean systolic blood pressure change

from baseline, mean fasting plasma glucose change from baseline, percentage of patients experiencing nausea and the percentage discontinuing treatment because of nausea, minor hypoglycaemia (events per patient per year), major hypoglycaemia, and other adverse events.

3.2 Three trials studied liraglutide as a triple therapy (that is, in addition to two oral therapies): LEAD-4, LEAD-5 and LEAD-6. The LEAD-6 trial compared liraglutide 1.8 mg with exenatide 10 micrograms, both in combination with metformin and/or a sulphonylurea. This study found liraglutide 1.8 mg to significantly reduce percentage HbA1c compared with exenatide (–1.12% versus –0.79% respectively). Weight reduced in both treatment groups but the difference was not statistically significant between the treatments (–3.24 kg with liraglutide 1.8 mg and –2.84 kg with exenatide). The LEAD-5 trial compared liraglutide 1.8 mg with insulin glargine and placebo in combination with metformin and a sulphonylurea. This trial showed liraglutide 1.8 mg reduced percentage HbA1c significantly compared with insulin glargine (–1.33% versus –1.09% respectively). Weight reduced in patients receiving liraglutide by 1.8 kg, whereas patients receiving insulin glargine gained 1.6 kg. The LEAD-4 trial compared liraglutide 1.2 mg and 1.8 mg with placebo. Liraglutide and placebo were given in combination with metformin and rosiglitazone. The results showed both liraglutide 1.2 mg and liraglutide 1.8 mg reduced HbA1c significantly compared with placebo (–1.5% [both doses] versus –0.5% respectively). Weight reduced in patients receiving liraglutide (–1.0 kg with liraglutide 1.2 mg and –2.0 kg with 1.8 mg), whereas patients receiving placebo gained 0.6 kg.

3.3 Three of the trials studied liraglutide in dual therapy in combination with either metformin or a sulphonylurea (1860, LEAD-1 and

LEAD-2). The 1860 trial compared liraglutide at doses of 1.2 mg and 1.8 mg with sitagliptin, all in combination with metformin. It found a greater improvement in glycaemic control (HbA1c reduction) with both doses of liraglutide than with sitagliptin. The study also found a significant reduction in weight with liraglutide: –3.0 kg with liraglutide 1.2 mg and –3.5 kg with liraglutide 1.8 mg, compared with sitagliptin (–1.0 kg). Another study (LEAD-1) compared liraglutide 0.6 mg, 1.2 mg and 1.8 mg with rosiglitazone and placebo. The study drugs were added to a sulphonylurea. All drug regimens significantly reduced HbA1c compared with placebo and the two higher liraglutide doses reduced HbA1c to a significantly greater extent than rosiglitazone. Although weight reduced in patients receiving liraglutide 1.8 mg (by –0.2 kg), weight increased with liraglutide 1.2 mg (by +0.3 kg). The third study (LEAD-2) compared liraglutide 0.6 mg, 1.2 mg and 1.8 mg with glimepiride and placebo. The study drugs were given in combination with metformin. This study found no significant difference between liraglutide and glimepiride in reducing percentage HbA1c. There was a statistically significant difference in change in weight between treatments: weight decreased with liraglutide (–1.8 kg with liraglutide 0.6 mg, –2.6 kg with liraglutide 1.2 mg and –2.8 kg with liraglutide 1.8 mg) and placebo (–1.5 kg) but increased with glimepiride (+1.0 kg).

- 3.4 The manufacturer reported that liraglutide has a good tolerability profile. The main adverse events reported during the clinical trials for liraglutide were gastrointestinal, followed by hypoglycaemia. The manufacturer's submission states that nausea was the most frequent adverse event identified with liraglutide treatment (1.2 or 1.8 mg).

- 3.5 The manufacturer identified one economic evaluation in its systematic review that projected the rates of mortality, diabetes complication and healthcare costs of liraglutide compared with rosiglitazone (both in addition to glimepiride) for type 2 diabetes, using a US healthcare payer perspective. Taking into account the setting of this economic evaluation, and the fact that drug costs were excluded from the analysis, the manufacturer submitted a de novo economic model (based on the CORE model).
- 3.6 The CORE diabetes model was used to predict the cost effectiveness of liraglutide in all of the comparisons presented in the manufacturer's submission. The CORE diabetes model is a non-product-specific diabetes policy analysis tool with a structure based on a series of 15 submodels that simulate the major complications of diabetes. Each submodel runs simultaneously and in parallel, thereby allowing patients to develop multiple complications, and uses time-, state-, time-in-state and diabetes type-dependent probabilities (where appropriate and available) to simulate the progress of patients through different health states.
- 3.7 The base-case assumptions used in the model incorporated a time horizon of 40 years. Treatment duration was set to 5 years (after which patients were assumed to have their treatment switched to a basal insulin regimen) in an attempt to replicate clinical practice. The modelling in NICE clinical guideline 87 on type 2 diabetes also used a treatment duration of 5 years. The manufacturer's analysis used health state utility values from five main published sources, taking into account a number of disease-related outcomes. Where possible, health state utilities were measured using the EQ-5D questionnaire and taken from a UK population with type 2 diabetes (mainly the United Kingdom Prospective Diabetes Study [UKPDS]). The manufacturer stated that in the CORE diabetes model, quality-

adjusted life years (QALYs) are calculated as a function of the states of diabetic complications reached during a given year of the simulation, with the addition of any acute events that may have occurred during that year. When a patient has more than one diabetic complication that has an associated utility value, the model selects the lowest value, and applies it for each year of the simulation (when no other medical events occur). If the patient experiences an event that has an associated disutility, the disutility is applied for that year.

- 3.8 The manufacturer reported that disutilities attributed to hypoglycaemia were derived from a study by Currie et al. (2006). In this study, data from 1305 UK patients with type 1 or type 2 diabetes were collected using both the Hypoglycaemia Fear Survey and the EQ-5D. Each severe hypoglycaemic event avoided was associated with a change of 5.9 on the Hypoglycaemia Fear Survey scale. The manufacturer also stated that the approach taken by NICE in the evaluation of exenatide in the NICE short clinical guideline on newer agents for the treatment of type 2 diabetes (CG87) also used utility estimates from Currie et al. (2006), based on the change of 5.9 points on the Hypoglycaemia Fear Survey scale. The manufacturer commented that a recently published literature review of BMI utility values was used to inform the decision on the appropriate BMI disutility. A disutility of  $-0.01$  per BMI unit over 25 was used in the base case. The manufacturer noted that in the model used to inform NICE clinical guideline 87, a utility value for BMI was taken from the CODE-2 study ( $-0.0061$  per BMI unit over 25). This value was not used in the original base case because it was not derived from UK patients; however, this value was used in the sensitivity analysis.



3.9 The manufacturer's submission presented the results as pairwise comparisons based on individual clinical trials against the comparator used in the relevant trial. The results from the manufacturer's submission were as follows:

- The comparison of liraglutide 1.8 mg with exenatide 10 micrograms (both drugs in combination with metformin and a sulphonylurea, based on the LEAD-6 trial) showed the incremental QALY gain was 0.163 with an incremental cost of £1638, resulting in an incremental cost-effectiveness ratio (ICER) of £10,054 per QALY gained for liraglutide.
- The comparison of liraglutide 1.8 mg with insulin glargine (both in combination with metformin and a sulphonylurea, based on the LEAD-5 trial) showed the incremental QALY gain was 0.241 with an incremental cost of £3638, resulting in an ICER of £15,130 per QALY gained for liraglutide.
- The comparison of liraglutide 1.2 mg and liraglutide 1.8 mg with sitagliptin 100 mg (all in combination with metformin, based on the 1860 trial) resulted in ICERs of £9851 (with an incremental QALY gain of 0.187 and incremental cost of £1842) and £10,465 per QALY gained (with an incremental QALY gain of 0.308 and incremental cost of £13224) for liraglutide 1.2 mg and 1.8 mg respectively.
- The comparison of liraglutide 1.2 mg and liraglutide 1.8 mg with rosiglitazone (all in combination with a sulphonylurea, based on the LEAD-1 trial) resulted in ICERs of £6226 (with an incremental QALY gain of 0.331 and incremental cost of £2064) and £9376 per QALY gained (with an incremental QALY gain of 0.398 and incremental cost of £3730) for liraglutide 1.2 mg and 1.8 mg respectively.
- The comparison of liraglutide 1.2 mg and liraglutide 1.8 mg with glimepiride (all in combination with metformin, based on the

LEAD-2 trial) resulted in ICERs of £13,257 (with an incremental QALY gain of 0.0.238 and incremental cost of £3157) and £19,837 per QALY gained (with an incremental QALY gain of 0.245 and incremental cost of £4858) for liraglutide 1.2 mg and 1.8 mg respectively.

- 3.10 The manufacturer supplied an incremental analysis of the cost effectiveness of liraglutide 1.8 mg relative to 1.2 mg. This produced results that differed significantly depending on the clinical trial chosen to perform the comparison. The analysis based on the 1860 trial gave an ICER of £11,414 per QALY gained for liraglutide 1.8 mg compared with 1.2 mg. However, in the analysis based on the LEAD-2 study, where the clinical-effectiveness results for liraglutide 1.2 mg and liraglutide 1.8 mg were similar, the cost per QALY gained for 1.8 mg compared with 1.2 mg increased to £249,494.
- 3.11 The manufacturer performed subgroup analyses based on BMI ( $\geq 30$  kg/m<sup>2</sup> and  $\geq 35$  kg/m<sup>2</sup>). An analysis of liraglutide compared with sitagliptin produced ICERs of £7593 per QALY gained (liraglutide 1.2 mg) and £8721 per QALY gained (1.8 mg) at a BMI greater than or equal to 30 kg/m<sup>2</sup>, and £6125 per QALY gained (1.2 mg) and £6091 per QALY gained (1.8 mg) at a BMI greater than or equal to 35 kg/m<sup>2</sup>. The manufacturer also compared liraglutide 1.8 mg with exenatide 10 micrograms, which produced ICERs of £11,535 per QALY gained at a BMI greater than or equal to 30 kg/m<sup>2</sup>, and £8555 per QALY gained at a BMI greater than or equal to 35 kg/m<sup>2</sup>. An analysis of liraglutide 1.8 mg compared with insulin glargine produced ICERs of £12,053 per QALY gained at a BMI greater than or equal to 30 kg/m<sup>2</sup>, and £9241 per QALY gained at a BMI greater than or equal to 35 kg/m<sup>2</sup>.

- 3.12 As part of the evidence base, the manufacturer included a submission to the Scottish Medicines Consortium (SMC), which used a treatment duration of 3 years and time horizon of 20 years (whereas the submission to NICE assumed a treatment duration of 5 years and time horizon of 40 years). There was a large difference in the ICERs presented in the two submissions for liraglutide second-line/dual therapy use compared with a sulphonylurea: £13,257 (1.2 mg, NICE submission) versus £23,598 (1.2 mg, SMC submission), and £19,837 (1.8 mg, NICE submission) versus £43,369 (1.8 mg, SMC submission). There were also differences in the submissions in relation to the other dual therapy regimens, all ICERs being higher in the SMC submission than in the NICE submission. There were also differences in the submissions in relation to triple therapy, but these differences were smaller than for dual therapy regimens.
- 3.13 The ERG did not consider that any relevant clinical-effectiveness studies of liraglutide had been excluded. The ERG noted that the submitted evidence of clinical effectiveness came mainly from the series of studies known as the LEAD programme. The ERG felt that all of the trials were of good quality, and that the analysis was fair and unbiased. However, the ERG commented that in LEAD-1, liraglutide was only compared with rosiglitazone 4 mg, although rosiglitazone is often used at a dosage of 8 mg daily. The ERG believed that pioglitazone would have been a better comparator because it might have a more favourable risk profile than rosiglitazone. The ERG noted that the average dose of insulin glargine in the LEAD-5 trial was 24 units a day, which the ERG considered to be low for the population of patients in the trial.
- 3.14 The ERG commented that the CORE model is a well-developed and well-respected diabetes model. The ERG noted that the CORE

model was also used for a previous technology appraisal submission ('Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus' [NICE technology appraisal guidance 151]). The ERG noted that within the CORE model there may be some concerns relating to the implementation of treatments after the initial treatment. If confirmed, this would not particularly affect the analyses relating to the comparisons of liraglutide with exenatide and sitagliptin, but would affect the analyses relating to insulin glargine. The ERG expressed concern that there are some uncertainties about cost effectiveness because of the need for long-term modelling based on data from short-term trials. The ERG commented that there may also be some concerns around the implementation of weight changes within the modelling. The duration of the direct benefits from initial treatments may have been too long, and the direct disutility associated with these changes may have been too large.

- 3.15 The ERG ran an exploratory analysis that used the cost of NPH insulin rather than the cost of insulin glargine when evaluating liraglutide 1.8 mg as a triple therapy compared with insulin. NICE clinical guideline 87 recommends NPH insulin as the first insulin therapy to try, and it also has a lower acquisition cost than insulin glargine. This analysis resulted in an ICER of £17,739 per QALY gained and was different to that estimated in the manufacturer's sensitivity analysis using the cost of NPH insulin (£24,933 per QALY gained). The difference was because the manufacturer had only used the NPH insulin cost in the comparator arm and not in the liraglutide 1.8 mg arm at year 5 when treatment changed to insulin (the cost of insulin glargine was still used in the liraglutide arm). The ERG used the NPH insulin costs in both arms of the model.

- 3.16 Exploratory sensitivity analyses undertaken by the ERG suggested that the main sources of the estimated patient benefits were: the direct utility effects of BMI changes and systolic blood pressure (for the comparison with insulin glargine), HbA1c (for the comparison with exenatide), and HbA1c and direct utility effects of BMI changes (for the comparison with sitagliptin).
- 3.17 In response to the first ACD consultation, the manufacturer provided a revised base-case analysis that incorporated an alternative assumption for the disutility associated with an increased BMI over 25 kg/m<sup>2</sup> of 0.0061 per unit (instead of 0.01). The revised base-case analysis also incorporated an alternative weight progression assumption whereby when treatment is switched, BMI reverts to baseline level and then increases as with insulin treatment. In the analysis for dual therapy, the revised base case resulted in increased ICERs (compared with the original base case) of £7545 per QALY gained for liraglutide 1.2 mg compared with rosiglitazone 4 mg (LEAD-1), £25,343 per QALY gained for liraglutide 1.2 mg compared with glimepiride 4 mg (LEAD-2), and £14,616 per QALY gained for liraglutide 1.2 mg compared with sitagliptin 100 mg (1860 trial).
- 3.18 The manufacturer also provided the revised base case for dual therapy stratified by BMI for liraglutide 1.2 mg compared with rosiglitazone 4 mg, liraglutide 1.2 mg compared with glimepiride 4 mg, and liraglutide 1.2 mg compared with sitagliptin 100 mg. The effect on the ICERs of increasing BMI did not follow a uniform pattern. In comparison with rosiglitazone in the LEAD-1 trial, the ICERs increased with increasing BMI so that the cost-effectiveness ratios were more favourable for liraglutide in patients with a BMI less than 30 kg/m<sup>2</sup> (£4911 per QALY gained) than in patients with a BMI greater than or equal to 35 kg/m<sup>2</sup> (£15,724 per QALY gained).

In comparison with glimepiride, the ICERs were more favourable for liraglutide in the  $\geq 30$  to  $< 35$  kg/m<sup>2</sup> BMI group (£25,413 per QALY gained) than in the higher BMI group ( $\geq 35$  kg/m<sup>2</sup>; £27,293 per QALY gained). When compared with sitagliptin in dual therapy, the ICER decreased with increasing BMI (liraglutide was dominated by sitagliptin for BMI  $< 30$  kg/m<sup>2</sup> and the ICER was £8347 per QALY gained for BMI  $\geq 35$  kg/m<sup>2</sup>).

- 3.19 The manufacturer presented new cost-effectiveness estimates for dual therapy treatment regimens which incorporated a 10-year treatment duration with a time horizon of 20 years, and a 10-year treatment duration with a time horizon of 40 years. This resulted in the ICERs increasing to £21,877 per QALY gained and £16,477 per QALY gained (liraglutide 1.2 mg versus rosiglitazone 4 mg, LEAD-1), £42,429 per QALY gained and £38,368 per QALY gained (liraglutide 1.2 mg versus glimepiride 4 mg, LEAD-2), £22,557 per QALY gained and £17,089 per QALY gained (liraglutide 1.2 mg versus sitagliptin 100 mg, 1860 trial) respectively.
- 3.20 The manufacturer also provided a mixed treatment comparison analysis to inform the relative effectiveness of liraglutide as part of triple therapy (compared with sitagliptin, rosiglitazone, exenatide and insulin glargine, all in combination with metformin and a sulphonylurea). The mixed treatment comparison used the six LEAD trials and the 1860 trial, and used the 26-week data from all trials (although LEAD-3 ran for 52 weeks). The manufacturer used an approach which allowed patient-level and trial-level covariates to be incorporated to estimate the treatment effects within trials. The results were then pooled across the network of trials. The trials included in the mixed treatment comparison were for both dual and triple therapy regimens. Therefore, it was assumed that the

treatment effects were comparable across trials using different regimens and independent of the stage of disease.

3.21 NICE asked the DSU to review the mixed treatment comparison that was provided by the manufacturer. The DSU noted that the mixed treatment comparison used the seven trials included in the original submission (LEAD-1 to 6 and the 1860 trial) but no consideration had been given to other potentially relevant trials. In addition, not all arms of the seven trials were included in the mixed treatment comparison. The ERG also commented on the lack of use of other relevant trials. The ERG noted that the only evidence for exenatide in the manufacturer's submission came from the LEAD-6 trial, even though there is a considerable body of other evidence on exenatide. The ERG also noted that there were trials comparing liraglutide with basal insulin, biphasic insulin once and twice daily, rosiglitazone, and a sulphonylurea (although there is currently no trial against a DPP-4 inhibitor). The DSU was concerned that the new analysis diverged considerably from a conventional mixed treatment comparison model. In particular, a mixed treatment comparison requires all treatment options to be connected. For this to happen in the manufacturer's mixed treatment comparison, further assumptions had to be made. The mixed treatment comparison included both dual therapy and triple therapy trials. Both the DSU and ERG expressed concern about one major assumption; that is, that a treatment has the same effect regardless of how many treatments and which treatments it is combined with (this was referred to as 'equality of effectiveness').

3.22 The manufacturer provided cost-effectiveness analyses for liraglutide 1.2 mg as a triple therapy, using the results of the mixed treatment comparison. The ICERs for liraglutide compared with rosiglitazone 4 mg, sitagliptin 100 mg, exenatide 10 micrograms

and insulin glargine were £10,876, £17,683, £5883 and £10,508 per QALY gained respectively.

- 3.23 The manufacturer provided an additional incremental analysis comparing the 1.8 mg liraglutide dose with the 1.2 mg dose, incorporating the revised base-case assumptions. This analysis gave ICERs of £13,057 (based on the 1860 trial) and £35,007 (based on LEAD-1) per QALY gained. For the analysis based on LEAD-2, the ICER presented was negative, indicating that liraglutide 1.8 mg was more costly and less effective than liraglutide 1.2 mg. When looking at the subgroup of patients whose BMI was greater than or equal to 35 kg/m<sup>2</sup>, the ICERs for liraglutide 1.8 mg compared with liraglutide 1.2 mg were £6828 (1860 trial), £7324 (LEAD-1) and £22,630 (LEAD-2) per QALY gained.
- 3.24 The results of a meta-analysis presented by the ERG showed no significant difference between liraglutide 1.2 mg and liraglutide 1.8 mg in terms of reduction in HbA1c level. The ERG noted that the ICERs varied widely for the analysis comparing liraglutide 1.8 mg with 1.2 mg in the subgroup with BMI greater than or equal to 35 kg/m<sup>2</sup> depending on which of the LEAD studies the data came from. The ERG commented that no ICER was provided using data from the LEAD-4 trial. The ERG noted that the results vary among trials, but it can be seen that in the higher BMI group (BMI ≥ 35 kg/m<sup>2</sup>), there were differences in HbA1c of 0.4% in LEAD-1 and 0.5% in 1860, these being the comparisons with the lower ICERs. Conversely, in LEAD-2, there was no difference in HbA1c, and the ICER based on that trial was much higher. In LEAD-4, which was the only trial of triple therapy in which the two doses were compared, there was no significant difference. The ERG noted the manufacturer's argument that the 1.8 mg dose has useful marginal effects over the 1.2 mg dose in the subgroup with



BMI of 35 kg/m<sup>2</sup> or over and that this may have some justification if liraglutide was approved for use in dual therapy. However, the ERG commented that there is a lack of evidence for benefit of using the larger dose in triple therapy.

3.25 The manufacturer proposed several explanations for the differences between the NICE and SMC submissions, including differences in treatment duration, time horizon, assumptions around switching treatment and HbA1c progression. The manufacturer explained that, for the SMC submission, treatment duration for liraglutide was set to 3 years because the exenatide submission to the SMC used 3 years. A 5-year treatment duration was chosen for the NICE submission after discussions with a panel of experts. The manufacturer also explained that the time horizon was increased in the NICE submission to meet the requirements of the NICE reference case, and capture the long-term costs and outcomes of treatment. The manufacturer stated that the assumptions used in the NICE submission were more appropriate. In the SMC submission, when treatment was switched, clinical parameters (blood pressure, lipids and weight) reverted back to their baseline values. However, the manufacturer commented that this did not happen in the analysis presented to NICE because it was difficult to make alterations to these parameters, there was no clinical evidence of what actually happens when treatment is switched, and a longer treatment duration was used in the NICE submission. The manufacturer stated that the UKPDS progression algorithm used in the NICE submission was a more robust method of approximating HbA1c progression than the method used in the SMC submission.

3.26 When comparing the differences between the NICE and SMC submissions reported by the manufacturer, the ERG noted that when the undiscounted life-expectancy difference was adjusted for

quality of life in the NICE submission (for analyses incorporating a 5-year treatment duration with 40-year time horizon), there were more QALYs than life years (about 30%). However, in the SMC version, adjustment for quality gave fewer QALYs than life years. The ERG noted that the explanation given by the manufacturer was unclear. However, the ERG felt that, overall, the explanations provided by the manufacturer seemed reasonable.

- 3.27 Full details of all the evidence are in the manufacturer's submission, the ERG report, and the DSU report, which are available from [www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)

## **4 Consideration of the evidence**

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of liraglutide, having considered evidence on the nature of type 2 diabetes and the value placed on the benefits of liraglutide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the current treatment options for people with type 2 diabetes and the current treatment pathway as outlined in NICE clinical guideline 87. The Committee heard from the clinical specialists and patient experts that type 2 diabetes is a progressive disease. The clinical specialists stated that the treatment is very complex and in clinical practice is based on the individual patient, focusing on what reduction in HbA1c can be achieved without weight gain or hypoglycaemia. The Committee heard about the strategies for managing type 2 diabetes that target both macrovascular and microvascular risk factors. Both the clinical specialists and patient experts highlighted the reluctance of people with type 2 diabetes to start insulin treatment because of the need

for multiple injections and regular blood glucose testing. The Committee noted that type 2 diabetes is a progressive disease and insulin treatment will inevitably be required when control with other agents, including GLP-1 analogues, becomes inadequate. It is acknowledged that liraglutide is the second GLP-1 analogue licensed, with exenatide already being available in NHS practice. It also noted that liraglutide could be either added to one oral agent (dual therapy) or added to two oral agents (triple therapy), and that there are several comparators at both these stages.

### ***Clinical effectiveness***

- 4.3 The Committee discussed the clinical studies of liraglutide as a triple therapy. It noted that the LEAD-6 trial (liraglutide 1.8 mg compared with exenatide) showed liraglutide was not significantly better than exenatide in reducing body weight or systolic blood pressure; however, there was a statistically significant difference in the mean HbA1c change from baseline in favour of liraglutide. The Committee also considered the comparison with insulin. It noted there was a statistically significantly greater reduction in HbA1c levels and in weight loss for liraglutide compared with insulin glargine. However, the Committee was aware that the LEAD-5 trial used a relatively low dose of insulin in the comparator arm, which may have affected the validity of the results relative to standard UK practice. It also noted that liraglutide in triple therapy, and the oral triple therapy regimens, would generally be considered for people who wished to delay insulin therapy, and the GLP-1 analogues were not a long-term substitute for insulin. The Committee concluded that in triple therapy, liraglutide showed some advantages over insulin, in particular its effect on weight relative to insulin, and noted the flexibility of taking liraglutide independently of meals which may have a positive effect on quality of life. The Committee also noted the advantage over exenatide with regards

to administration, with liraglutide requiring a once-daily injection compared with twice daily for exenatide.

4.4 The Committee discussed the mixed treatment comparison submitted by the manufacturer which analysed the relative effectiveness of liraglutide and the other triple therapy options. The Committee noted the concern expressed by the ERG and DSU about the lack of direct trial comparisons and the assumption of 'equality of effectiveness' (see section 3.21). The Committee heard from the clinical specialists that the magnitude of satisfactory response tends to be within a range of 1.0–1.5% reduction in HbA1c, but that the treatment effects/response are not necessarily constant at different stages in the treatment pathway (that is, the response tends to be greater earlier in the treatment pathway, at a less advanced stage of disease). The response rate, which is the number of people treated who show therapeutic benefit, is also not necessarily independent of disease stage. The Committee concluded that pooling the overall effects for treatments in both dual and triple therapy regimens was therefore not appropriate given that type 2 diabetes is a progressive condition, and it cannot be assumed that treatment effects are comparable across different treatments and disease stages. The Committee also had concerns about the assumption that the therapeutic effect of a drug would be the same independent of the drug combination in which it was used. Overall, the Committee had serious reservations about the assumptions used in the mixed treatment comparison. The Committee also noted that the mixed treatment comparison ignored a significant body of clinical data for thiazolidinediones, DPP-4 inhibitors and exenatide. The Committee concluded that the underlying assumptions used for the mixed treatment comparison were associated with a large amount of uncertainty, and therefore considered that its conclusions could not be regarded as robust.

- 4.5 The Committee discussed the use of liraglutide as a component of dual therapy. The clinical specialists stated that the longer-term beneficial effects of a GLP-1 analogue may be greater when used earlier in the treatment pathway. They also commented that if weight is lost in the early stages of the disease, beta-cell depletion may be less severe (beta-cell function decreases with time) and they referred to preliminary data that suggest that GLP-1 analogues may be more effective when introduced earlier in the treatment pathway. The Committee heard from the clinical specialists that the potential benefits on macrovascular disease, the risk of which is lowered by tight control of HbA1c, are greater in younger people with type 2 diabetes and no comorbidities. Clinical specialists commented that the prevalence of hypoglycaemia is important and it was noted that approximately 25% of people being treated with a sulphonylurea experience hypoglycaemia.
- 4.6 The Committee noted that appropriate comparators for liraglutide in a dual therapy regimen were sulphonylureas, thiazolidinediones and DPP-4 inhibitors. NICE clinical guideline 87 recommends metformin as the usual first-line therapy followed by one of these drug classes if metformin provides insufficient control of HbA1c.
- 4.7 The Committee discussed the trials of liraglutide in dual therapy. The Committee noted that the LEAD-1 trial (liraglutide plus sulphonylurea compared with rosiglitazone plus sulphonylurea) showed that liraglutide resulted in a greater reduction in HbA1c than rosiglitazone but that the comparator drug was only used at a dose of 4 mg. The clinical specialists stated that approximately 10–15% of people would be treated with the combination of sulphonylurea and a thiazolidinedione, of whom the majority would receive pioglitazone rather than rosiglitazone, and that some of those treated with rosiglitazone would be taking an 8 mg dose

rather than the 4 mg dose used in the trial. The Committee heard from the clinical specialists that the increased HbA1c response with the 8 mg dose reported in some studies is not seen in clinical practice, and that when rosiglitazone is prescribed, the 4 mg dose is most commonly used. However, the Committee concluded that it was unclear whether or to what extent the trial data using rosiglitazone at a dose of 4 mg in combination with a sulphonylurea were generalisable to all patients taking a thiazolidinedione as part of dual therapy.

- 4.8 The Committee discussed the LEAD-2 results, which showed that liraglutide given with metformin had no greater effect on HbA1c than glimepiride given with metformin, although there were body weight and modest blood pressure benefits with liraglutide. The Committee considered that the lack of superiority of liraglutide over sulphonylureas in terms of improved glycaemic control would indicate that the justification for replacing well-established standard therapy with a new injectable agent would be entirely based on factors other than control of blood sugar, such as effects on weight and the potential risk of hypoglycaemia.
- 4.9 The Committee noted that the 1860 trial (comparing liraglutide with sitagliptin, both in combination with metformin) showed that liraglutide achieved greater reduction in HbA1c and also a significantly greater weight loss than sitagliptin. It also noted however, that the benefit of liraglutide compared with sitagliptin in relation to HbA1c reduction was only modest at 0.34% (1.24% with liraglutide 1.2 mg compared with 0.9% reduction with sitagliptin).
- 4.10 The Committee considered that although LEAD-2 showed no beneficial effect on glycaemic control relative to glimepiride, the body weight benefits associated with liraglutide were more consistent across the dual therapy trials. Both clinical specialists

and patient experts emphasised the importance of weight loss to people with type 2 diabetes. The Committee understood that the benefits of weight loss are not uniform (greater benefits may be achieved in those with a higher BMI at the start of treatment). The Committee noted that weight is also a surrogate endpoint for cardiovascular risk but is not directly related to mortality risk as an independent variable in diabetes. The Committee noted the evidence from the clinical studies that showed liraglutide had advantages in terms of weight loss when compared with certain therapies, notably those associated with weight gain such as sulphonylureas and insulin. The Committee acknowledged that the effect on body weight was an important consideration when choosing treatments for diabetes. However, the Committee concluded that the primary aim of any diabetes medication must be glycaemic control, which was also the primary endpoint in the trials. Although other benefits related to weight loss and blood pressure may be of value to patients, they are secondary outcomes for which alternative treatments and approaches are available. The Committee also heard from clinical specialists that there is a small group of patients who are unable to take multiple oral therapy options, because of intolerance or contraindications, resulting in a requirement for the early initiation of insulin and for whom a GLP-1 analogue may be appropriate as part of dual therapy.

- 4.11 The Committee discussed the results of the clinical trials that compared liraglutide 1.2 mg with liraglutide 1.8 mg. The Committee heard from clinical specialists that the majority of patients in clinical practice receive liraglutide 1.2 mg, with no more than 10% receiving 1.8 mg (daily). The manufacturer estimated that, on the basis of their experience in the UK market, only 5% of people receive the 1.8 mg dose. The Committee noted that the results of a meta-analysis presented by ERG showed no significant difference

between liraglutide 1.2 mg and liraglutide 1.8 mg in terms of HbA1c reduction. The Committee also noted that no clinical trial has evaluated the effects of dose escalation of liraglutide from 1.2 mg to 1.8 mg, and it heard from the clinical specialists that there is limited experience of dose escalation in clinical practice. Given that there was no robust evidence of additional benefits on glycaemic control from a higher dose, and the lack of clinical trials investigating dose escalation, the Committee concluded that treatment with liraglutide 1.8 mg was not justified.

4.12 The Committee noted the limitations of the trials, in that they were short-term trials with several parallel groups and relatively small numbers of patients in each group. The Committee was aware that because the trials were too short to capture long-term outcome data, surrogate endpoints had been used. The sample size calculations had also been based on these surrogate endpoints rather than being powered to show differences in clinical events. The Committee concluded that this added considerable uncertainty to the estimation of the overall benefits of treatment.

4.13 The Committee discussed the adverse effects associated with liraglutide and noted that the most common adverse effect reported in the clinical trials was nausea, and that the number of cases of pancreatitis was consistent with the predicted rate in type 2 diabetes. The manufacturer commented that the incidence of pancreatitis was low in patients with type 2 diabetes who were treated with liraglutide. They added that no cases of pancreatitis have been reported among the UK patients being treated with liraglutide (approximately 14,000). The Committee concluded that the short-term adverse-effect profile of liraglutide appeared acceptable. It noted that long-term safety data were not yet available.



**Cost effectiveness**

- 4.14 The Committee discussed the economic analyses presented that compared liraglutide in triple therapy compared with either insulin glargine (LEAD-5) or exenatide (LEAD-6). The Committee discussed insulin glargine as a comparator, and whether NPH insulin would have been more appropriate, as recommended in NICE clinical guideline 87. It heard from the clinical specialists that most clinicians use insulin glargine, and that long-acting insulin analogues (insulin glargine and insulin detemir) account for the majority of basal insulin use in the UK. The Committee noted that the ICERs were within the range normally considered cost effective but that the average dose of insulin glargine used in LEAD-5 was 24 units, which could be considered lower than would be used in clinical practice and could have an effect on the cost-effectiveness estimate. The Committee took into account the views from the clinical specialists and patient experts that there are fewer treatment choices later in the treatment pathway, and that people are often reluctant to move on to treatment with insulin. However, the Committee noted that there were several other alternatives to moving on to insulin therapy, which included the addition of a third oral therapy (thiazolidinediones or DPP-4 inhibitors).
- 4.15 The Committee was aware that no direct trial evidence was available comparing liraglutide with thiazolidinediones and DPP-4 inhibitors as alternative components of triple therapy regimens. The Committee acknowledged the attempt to address this in the mixed treatment comparison and the subsequent cost-effectiveness analysis comparing liraglutide with rosiglitazone and sitagliptin. The Committee noted the comments of the DSU on the mixed treatment comparison and the assumptions used to underpin the comparisons. It felt that the unconventional methodology used for the mixed treatment comparison and the assumptions used to

underpin the comparisons created uncertainty in the cost-effectiveness estimates presented. The Committee therefore concluded that the evidence provided was not robust enough to allow it to recommend liraglutide as a cost-effective alternative to either thiazolidinediones, particularly pioglitazone, or DPP-4 inhibitors in triple therapy regimens.

4.16 The Committee was aware of the current recommendation for the use of exenatide (twice daily) in NICE clinical guideline 87 and the restrictions in the recommendation, and accepted that this reflected current clinical practice. The Committee considered that where exenatide would be recommended in NICE clinical guideline 87, liraglutide would be a cost-effective alternative, with an ICER of £10,100 per QALY gained (although the Committee noted that this ICER related to liraglutide 1.8 mg). The Committee discussed the comments received following the ACD consultation that suggested including 'reluctance to start insulin treatment' for people with a BMI < 35 kg/m<sup>2</sup>, however the Committee agreed that this group was not easy to identify. The Committee therefore concluded that liraglutide in triple therapy regimens was an appropriate alternative to exenatide if used as described for exenatide in NICE clinical guideline 87, including the criteria for assessing whether the patient's condition was responding to therapy at 6 months and could therefore continue treatment, and should be recommended as a triple therapy option within these restrictions.

4.17 The Committee considered the ICERs against the relevant comparators in dual therapy regimens. The Committee noted that sensitivity analyses showed the main driver of cost effectiveness to be decreases in HbA1c and that benefits relating to weight loss and blood pressure were incorporated. The Committee noted that the submission made by the manufacturer to the SMC (provided by the

manufacturer to NICE as an appendix to their clarification response) gave results for dual therapy that were considerably different from those presented in the submission to NICE. It was noted that the submission to NICE used a time horizon of 40 years and treatment duration of 5 years, whereas the submission to the SMC used a time horizon of 20 years and treatment duration of 3 years. The Committee understood that increasing the time horizon parameter would be expected to decrease the ICER. Likewise, increasing the treatment duration would be expected to increase the ICER. The manufacturer initially stated that the higher ICER presented to the SMC for the comparison with sulphonylureas was calculated using the whole patient cohort of the LEAD-2 trial, whereas the lower ICER presented to NICE was calculated using a subgroup of the trial. This subgroup included one-third of the patients from the cohort who were receiving treatment with one oral agent at the start of the trial. However, the manufacturer later clarified that this was not the reason for the differences in the results, and that they were due in part to the effects on blood pressure, lipids and weight at the point of switching treatment being different in the SMC model compared with the NICE model. The rate of calculated HbA1c change with time also differed between the SMC and NICE model parameters. The Committee concluded that there still remained uncertainty as to why the estimates between the two submissions differed and that it was not possible to be confident that the lower ICERs presented to NICE were the more reliable.

- 4.18 The Committee considered the new base-case analyses for dual therapy presented by the manufacturer, which incorporated the alternative assumption of 0.0061 (from CODE-2) disutility per unit BMI change over 25 kg/m<sup>2</sup> (instead of 0.01 from the LEAD trials) and an alternative weight progression assumption (when treatment

was switched, BMI reverted to baseline level and then increased as with insulin treatment). The Committee noted that the ICERs increased from £6230 to £7550 (liraglutide compared with rosiglitazone), from £13,300 to £25,300 (liraglutide compared with glimepiride), and from £9850 to £14,600 (liraglutide compared with sitagliptin). The Committee also noted that when the analyses were stratified by BMI, the results were not as expected (treatment with liraglutide was expected to be more cost effective in patients with a high BMI), except for the comparison with sitagliptin. However, the Committee noted that this variability may be due to the small number of patients in each BMI group in the analysis.

- 4.19 The Committee discussed the new results presented by the manufacturer, which incorporated a 10-year treatment duration with a time horizon of 20 years, and a 10-year treatment duration with a time horizon of 40 years, and noted the significant increase in the ICERs compared with those presented in the original submission. The ICERs increased to £21,900 per QALY gained and £16,500 per QALY gained (liraglutide 1.2 mg versus rosiglitazone 4 mg, LEAD 1), £42,400 per QALY gained and £38,400 per QALY gained (liraglutide 1.2 mg versus glimepiride 4 mg, LEAD-2), £22,600 per QALY gained and £17,000 per QALY gained (liraglutide 1.2 mg versus sitagliptin 100 mg, 1860 trial) respectively. The Committee noted that treatment duration had a significant effect on the cost-effectiveness estimates, and is likely to vary depending on the stage of the disease at which treatment is started. It concluded that there remains uncertainty about treatment duration, but if treatment was started earlier in the course of the disease this could result in treatment periods being longer than estimated in the base-case analysis, with resulting increases in the ICERs.

- 4.20 The Committee was mindful that the analyses presented in the manufacturer's submission departed from the NICE reference case, which specifies that the economic analysis should take into account parameter uncertainty (probabilistic analysis). The Committee noted that uncertainty in patient baseline characteristics was only included as a one-way sensitivity analysis rather than as the base case. In addition, the many rate parameters in the risk equations were not represented at all. The Committee was not persuaded that the number of uncertain parameters was a sufficient reason for not taking their uncertainty into account. The Committee therefore concluded that the results of the economic analysis should be interpreted with caution.
- 4.21 The Committee was mindful that a very large number of people receive dual therapy regimens for diabetes, so there needs to be a high degree of certainty in introducing new treatments at this stage. The Committee further noted the lack of long-term safety data associated with liraglutide and that liraglutide is an injected agent, whereas current dual therapy options are oral therapies.
- 4.22 Taking into account all the evidence on the clinical and cost effectiveness, and the uncertainty around the data presented, the Committee concluded that liraglutide 1.2 mg could not be recommended over the other options available as part of a dual therapy regimen. The Committee discussed whether liraglutide should be an option for those people unable to take multiple oral therapy options and whose only current alternative treatment was the early initiation of insulin. It agreed that there was a potential clinical need for those people who were either intolerant to multiple oral therapy options or treatment with these options was contraindicated. The Committee discussed whether the word 'unsuitable' would be more appropriate than 'contraindicated', but

concluded that this had a less precise definition and was open to misinterpretation. The Committee therefore concluded that liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) should be recommended as an option for the treatment of people with type 2 diabetes, only if:

- the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin **or** a sulphonylurea is contraindicated, **and**
- the person is intolerant of thiazolidinediones **and** DPP-4 inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

4.23 The Committee discussed the manufacturer's incremental economic analysis, which compared liraglutide 1.8 mg with liraglutide 1.2 mg. It noted that the results differed markedly depending on the clinical trial on which the analysis was based. The Committee also noted the cost-effectiveness results comparing liraglutide 1.8 mg with liraglutide 1.2 mg for those people with a BMI greater than or equal to 35 kg/m<sup>2</sup>, with ICERs ranging from £6800 per QALY gained (1860 trial) to £22,600 per QALY gained (LEAD-2 trial). The Committee was aware that there is limited clinical experience of dose escalation with liraglutide (see section 4.11). Taking into account the lack of clinical trial evidence showing a significant benefit from increasing the liraglutide dose from 1.2 mg to 1.8 mg, the widely varying ICERs and the uncertainty in the economic analysis, the Committee concluded that liraglutide 1.8 mg would not be a cost-effective use of NHS resources, and therefore should not be recommended for the treatment of type 2 diabetes.

4.24 The Committee discussed how adequate response to treatment with liraglutide would be defined to determine if treatment should be

continued. The Committee agreed that it would be reasonable to have treatment discontinuation criteria for non-responders to treatment, as currently responders and non-responders (to GLP-1 analogues) cannot be identified until the treatment has been started. It was aware of the continuation rule for exenatide in NICE clinical guideline 87, which states that treatment should only be continued if the person has had a beneficial metabolic response, defined as a reduction of at least 1 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months. Several alternative wording suggestions were made, including using 'or' instead of 'and' in the requirements for HbA1c and weight loss. The Committee accepted that the relationship between HbA1c reduction and weight loss may be independent variables. However, it did not consider that weight loss alone was a satisfactory therapeutic outcome. Although acknowledging the heterogeneity of the patient population and their differing response to this agent, the Committee did not consider that there were any specific features of liraglutide that justified different continuation criteria from the other GLP-1 analogue currently recommended by NICE. Furthermore, the calculated cost-effectiveness ratios of the GLP-1 analogues would only apply if the duration of treatment was the same. For dual therapy regimens, the Committee thought it reasonable that a similar continuation rule should apply, but noted that the criterion of weight loss may not be applicable to non-obese patients. Therefore, the Committee agreed that liraglutide as a dual therapy should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c) at 6 months.

- 4.25 The Committee was aware that there may be people with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in the recommendations for dual or triple therapy (see

sections 1.1 and 1.3), or who are receiving liraglutide 1.8mg. The Committee agreed that these people should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop, and that this should be included in the recommendations.

**Summary of Appraisal Committee’s key conclusions**

TAXXX (STA)	Appraisal title: Liraglutide for the treatment of type 2 diabetes	FAD section
<b>Key conclusion</b>		
Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in ‘Type 2 diabetes: the management of type 2 diabetes’ (NICE clinical guideline 87).		1.1
Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if the person is intolerant of either metformin or a sulphonylurea, or treatment with metformin or a sulphonylurea is contraindicated, and the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones and DPP-4 inhibitors is contraindicated.		1.3
Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.		1.5
The Committee concluded that the evidence provided was not robust enough to allow it to recommend liraglutide as a cost-effective alternative to either thiazolidinediones or DPP-4 inhibitors as a triple therapy regimen, however it believes liraglutide is a cost-effective treatment option relative to exenatide.		4.15 and 4.16
Taking into account the uncertainty around the data presented, liraglutide 1.2 mg could not be recommended over the other options available for dual therapy regimens.		4.22
Taking into account the lack of clinical trial evidence showing a significant benefit from increasing the liraglutide dose from 1.2 mg to 1.8 mg, the widely varying ICERs and the uncertainty in the economic analysis, the Committee was unable to recommend liraglutide 1.8 mg for the treatment of type 2 diabetes.		4.23
The Committee concluded that people with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in section 1.1 or 1.3, or who are receiving liraglutide 1.8 mg, should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.		1.6 and 4.25



Current practice		
Clinical need of patients, including the availability of alternative treatments	Type 2 diabetes is a progressive disease. Treatment is very complex and in clinical practice is based on the individual patient, focusing on what reduction in HbA1c can be achieved without weight gain or hypoglycaemia. Current strategies for managing type 2 diabetes target both macrovascular and microvascular risk factors.	4.2
	Available alternatives in dual therapy regimens include sulphonylureas, thiazolidinediones and DPP-4 inhibitors (given that NICE clinical guideline 87 recommends metformin as the usual first-line therapy followed by one of these drug classes).	4.6
	There are fewer treatment choices available later in the treatment pathway, and people are often reluctant to move on to treatment with insulin. However, the Committee agreed that this group was not easy to identify.	4.14 and 4.16
The technology		
Proposed benefits of the technology	The Committee noted that liraglutide is the second GLP-1 analogue available, alongside exenatide.	4.2
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Liraglutide may have some advantages over exenatide and insulin, in particular its effect on weight relative to insulin, and also because it is a once-daily injection compared with twice daily for exenatide.	4.3
What is the position of the treatment in the pathway of care for the condition?	Liraglutide could be either added to one oral agent (dual therapy) or added to two oral agents (triple therapy).	4.2
Adverse effects	The most common adverse effect reported in the clinical trials was nausea, and the number of cases of pancreatitis was consistent with the predicted rate in type 2 diabetes. The Committee concluded that the short-term adverse-effect profile of liraglutide appeared acceptable. It noted that long-term safety data are not yet available.	4.13

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the LEAD-6 trial (liraglutide 1.8 mg compared with exenatide) showed liraglutide was not significantly better than exenatide in reducing body weight or systolic blood pressure; however, there was a statistically significant difference in the mean HbA1c change from baseline in favour of liraglutide. The Committee noted there was a statistically significantly greater reduction in HbA1c levels and in weight loss for liraglutide compared with insulin glargine.	4.3
	The Committee noted that the LEAD-1 trial showed that higher doses of liraglutide were superior to rosiglitazone but also noted that the comparator drug was used at a low dose.	4.7
	The Committee noted that the LEAD-2 trial showed that liraglutide and glimepiride had similar effects on HbA1c but there was more weight gain with glimepiride.	4.8
	The Committee noted that the 1860 trial showed that liraglutide achieved greater reduction in HbA1c and also a significantly greater weight loss than sitagliptin.	4.9
	The Committee concluded that liraglutide is effective in terms of glycaemic control and was associated with beneficial effects on body weight relative to some other comparators.	4.9 and 4.10
	The Committee considered the comparisons with insulin glargine presented by the manufacturer. However, the Committee noted that there were other alternatives to moving on to insulin therapy such as the addition of a third oral therapy (thiazolidinediones or DPP-4 inhibitors), and that no direct trial evidence was available comparing liraglutide with these alternative triple therapy regimens.	4.14 and 4.15
	The trials were short-term trials with several parallel groups, had relatively small numbers of patients in each group, used surrogate endpoints, and the sample size calculations had been based on these rather than being powered to show differences in clinical events. The Committee concluded that this added considerable uncertainty to the estimation of the overall benefits of treatment.	4.12

	The LEAD-5 trial used a relatively low dose of insulin, which may have affected the validity of the results relative to standard UK practice.	4.3
Relevance to general clinical practice in the NHS	(See the technology section above)	4.2 and 4.3
Uncertainties generated by the evidence	<p>The trials were short-term, with several parallel groups, relatively small numbers of patients in each group and surrogate endpoints. The sample size calculations had been based on these rather than being powered to show differences in clinical events. The Committee concluded that this added considerable uncertainty to the estimation of the overall benefits of treatment.</p> <p>There is currently no direct trial evidence available comparing liraglutide with thiazolidinediones or DPP-4 inhibitors as alternative components of triple therapy regimens.</p>	4.12  4.15
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee understood that the benefits of weight loss are not uniform (greater benefits may be achieved in those with a higher BMI at the start of treatment).	4.10
Estimate of the size of the clinical effectiveness including strength of supporting evidence	<p>In triple therapy, liraglutide showed some advantages over insulin and exenatide, in particular its effect on weight relative to insulin, and also the once-daily injection administration compared with twice daily for exenatide.</p> <p>However, there is a lack of direct trial evidence of liraglutide in triple therapy regimens. Additional analysis submitted by the manufacturer did not clarify the uncertainty around the effectiveness of liraglutide in triple therapy regimens.</p> <p>There were no clinical trials which evaluated the effects of dose escalation, and no robust evidence of additional benefits of increasing the dose of liraglutide from 1.2 mg to 1.8 mg.</p> <p>There are several limitations of the trial evidence considered which adds considerable uncertainty to the estimation of the overall benefits of treatment.</p>	4.3  4.4  4.11  4.12

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee did not make any conclusions on this aspect.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>New base-case analyses submitted by the manufacturer also added uncertainty; analyses were stratified by BMI, and the results were not as expected (treatment with liraglutide was expected to be more cost effective in patients with a high BMI), except for the comparison with sitagliptin.</p> <p>The unconventional methodology used in the mixed treatment comparison evaluating liraglutide in triple therapy regimens, and the assumptions used to underpin the comparisons created uncertainty around the cost-effectiveness estimates presented.</p> <p>There was considerable uncertainty around the differences in cost-effectiveness estimates between the submissions to NICE and the SMC.</p>	<p>4.18</p> <p>4.4, 4.15</p> <p>4.17</p>
<p>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	The Committee did not make any conclusions on this aspect.	
Are there specific groups of people for whom the technology is particularly cost effective?	<p>Subgroup analyses by BMI suggested that for patients with a higher BMI, liraglutide was typically more cost effective.</p> <p>The results of the new economic analyses by subgroup according to BMI (BMI &lt; 30 kg/m<sup>2</sup>, BMI ≥ 30 kg/m<sup>2</sup> to &lt; 35 kg/m<sup>2</sup>, and BMI ≥ 35 kg/m<sup>2</sup>) were not as expected (the treatment option was expected to be more cost effective in patients with a high BMI), except for the comparison with sitagliptin.</p>	<p>3.11</p> <p>4.18</p>

What are the key drivers of cost effectiveness?	For dual therapy regimens, sensitivity analyses showed the main driver of cost effectiveness was a large decrease in HbA1c, and that benefits relating to weight loss are also a factor in driving the cost effectiveness.	4.17
Most likely cost-effectiveness estimate (given as an ICER)	There were many ICERs presented for different comparisons.	3.9
	For liraglutide versus exenatide (triple therapy), the Committee accepted the ICER of £10,100 per QALY gained (although the Committee noted that this ICER related to liraglutide 1.8 mg).	4.16
	The Committee did not consider the ICERs presented for other oral therapies in both dual and triple therapy regimens to be robust enough to allow them to recommend liraglutide as a cost-effective alternative.	4.15 and 4.22
	The Committee noted the lack of clinical trial evidence showing a significant benefit from increasing the liraglutide dose from 1.2 mg to 1.8 mg, the widely varying ICERs and the uncertainty in the economic analysis. The Committee concluded that liraglutide 1.8 mg would not be a cost-effective use of NHS resources, and therefore was not recommended.	4.23
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations	The restrictions outlined in the recommendations and also in NICE clinical guideline 87 ('Type 2 diabetes: the management of type 2 diabetes') incorporate appropriate adjustment of BMI by ethnic group.	1.1

## 5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website ([www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)). [NICE to amend list as needed at time of publication]
- Slides highlighting key messages for local discussion.
  - Costing report and costing template to estimate the savings and costs associated with implementation.
  - Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
  - A costing statement explaining the resource impact of this guidance.
  - Audit support for monitoring local practice.

## 6 Related NICE guidance

### Published

- Type 2 diabetes: newer agents (partial update of CG66). NICE clinical guideline 87 (2009). Available from [www.nice.org.uk/guidance/CG87](http://www.nice.org.uk/guidance/CG87)

- Continuous subcutaneous insulin infusion for the treatment of diabetes (review). NICE technology appraisal guidance 151 (2008). Available from [www.nice.org.uk/guidance/TA151](http://www.nice.org.uk/guidance/TA151)
- Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66 (2008). Available from [www.nice.org.uk/guidance/CG66](http://www.nice.org.uk/guidance/CG66)
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008). Available from [www.nice.org.uk/guidance/CG63](http://www.nice.org.uk/guidance/CG63)
- Inhaled insulin for the treatment of type 1 and type 2 diabetes. NICE technology appraisal guidance 113 (2006). Available from [www.nice.org.uk/guidance/TA113](http://www.nice.org.uk/guidance/TA113)
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from [www.nice.org.uk/guidance/CG10](http://www.nice.org.uk/guidance/CG10)
- Glitazones in the treatment of type 2 diabetes (review of TA9 and TA21). NICE technology appraisal guidance 63 (2003). Available from [www.nice.org.uk/guidance/TA63](http://www.nice.org.uk/guidance/TA63)
- Diabetes (types 1 and 2) – patient education models. NICE technology appraisal guidance 60 (2003). Available from [www.nice.org.uk/guidance/TA60](http://www.nice.org.uk/guidance/TA60)
- Diabetes (types 1 and 2) – long-acting insulin analogues. NICE technology appraisal guidance 53 (2002). Available from [www.nice.org.uk/guidance/TA53](http://www.nice.org.uk/guidance/TA53)

## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in May 2012 to coincide with the review of NICE clinical guideline 87. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam  
Chair, Appraisal Committee A  
September 2010



## **Appendix A: Appraisal Committee members and NICE project team**

### **A      *Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE.

Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Jane Adam (Chair)**

Department of Diagnostic Radiology, St George's Hospital

#### **Professor A E Ades**

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

#### **Mrs Elizabeth Brain**

Lay member

#### **Professor Karl Claxton**

Professor of Health Economics, University of York

**Dr Fiona Duncan**

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

**Mr Christopher Earl**

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

**Dr Paul Ewings**

Statistician, Taunton & Somerset NHS Trust, Taunton

**Mr John Goulston**

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

**Mr Adrian Griffin**

VP Strategic Affairs, LifeScan, Johnson & Johnson

**Dr Terry John**

General Practitioner, The Firs, London

**Dr Alec Miners**

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

**Dr Ann Richardson**

Lay member

**Mr David Thomson**

Lay member

**Mr William Turner**

Consultant Urologist, Addenbrooke's Hospital

**Dr Luke Twelves**

General Practitioner, Ramsey Health Centre, Cambridgeshire

**Mr Mike Spencer**

General Manager, Cardiff and Vale University Health Board – Facilities and Clinical Support Services

**Dr David Newsham**

Lecturer (Orthoptics), University of Liverpool

**Mrs Angela Schofield**

Chairman, Bournemouth and Poole Teaching PCT

**Professor Iain Squire**

Consultant Physician, University Hospitals of Leicester

**Dr Peter Heywood**

Consultant Neurologist, Frenchay Hospital

**Dr Ian Lewin**

Consultant Endocrinologist, North Devon District Hospital

**Dr Louise Longworth**

Reader in Health Economics, HERG, Brunel University

**Dr Anthony S Wierzbicki**

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

**Professor Jonathan Grigg**

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

**Dr John Watkins**

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

**Dr Nick Murray**

Senior Lecturer and Consultant in Medical Oncology, University of Southampton

**Dr Olivia Wu**

Reader in Health Economics, University of Glasgow

**B**      ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Carina Righetti**

Technical Lead

**Helen Knight**

Technical Adviser

**Bijal Joshi**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Cummins E, et al., Evidence review: liraglutide for the treatment of type 2 diabetes, December, 2009

B The Decision Support Unit (DSU) report for this appraisal was prepared by Alex Sutton, Professor of Medical Statistics, University of Leicester.

C The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Novo Nordisk

II Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- Diabetes Research & Wellness Foundation
- Diabetes UK
- National Diabetes Nurse Consultant Group
- Royal College of Nursing
- Royal College of Physicians
- South Asian Health Foundation

III Other consultees:

- Department of Health
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety - Northern Ireland
- Eli Lilly and Company
- GlaxoSmithKline
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals
- Pfizer
- Takeda UK

D The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on liraglutide by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Stephen Charles Bain, Professor of Medicine (Diabetes) & Honorary Consultant Physician, ABM University NHS Trust, nominated by Association of British Clinical Diabetologists – clinical specialist
- Professor Jiten Vora, Consultant Endocrinologist/Diabetologist, Royal Liverpool University Hospital, nominated by Diabetes UK – clinical specialist
- Ms Beryl McCorkle, Manager/retired, nominated by Diabetes UK – patient expert
- Mrs Juliette Rosemary Farthing, UK Vice Chair of East Suffolk Diabetes User Group, nominated by Diabetes UK – patient expert

E Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. As a consultee, the manufacturer/sponsor was also invited to comment on the ACD.

- Novo Nordisk