Liraglutide for the treatment of type 2 diabetes

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of liraglutide in the treatment of type 2 diabetes mellitus, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The manufacturer proposed the use of liraglutide as a second or third drug in patients with type 2 diabetes whose glycaemic control was unsatisfactory with metformin, with or without a second oral glucose-lowering drug. The submission included six manufacturer-sponsored trials that compared the efficacy of liraglutide against other glucose-lowering agents. Not all of the trials were relevant

to the decision problem. The most relevant were Liraglutide Effects and Actions in Diabetes 5 (LEAD-5) (liraglutide used as part of triple therapy and compared against insulin glargine) and LEAD-6 [liraglutide in triple therapy compared against another glucagon-like peptide-1 agonist, exenatide]. Five of the six trials were published in full and one was then unpublished. Two doses of liraglutide, 1.2 and 1.8 mg, were used in some trials, but in the two comparisons in triple therapy, against glargine and exenatide, only the 1.8-mg dose was used. Liraglutide in both doses was found to be clinically effective in lowering blood glucose concentration [glycated haemoglobin (HbA_{1c})], reducing weight (unlike other glucose-lowering agents, such as sulphonylureas, glitazones and insulins, which cause weight gain) and also reducing systolic blood pressure (SBP). Hypoglycaemia was uncommon. The ERG carried out meta-analyses comparing the 1.2- and 1.8-mg doses of liraglutide, which suggested that there was no difference in control of diabetes, and only a slight difference in weight loss, insufficient to justify the extra cost. The cost-effectiveness analysis was carried out using the Center for Outcomes Research model. The health benefit was reported as quality-adjusted life-years (QALYs). The manufacturer estimated the cost-effectiveness to be £15,130 per QALY for liraglutide 1.8 mg compared with glargine, £10,054 per QALY for liraglutide 1.8 mg compared with exenatide, £10,465 per QALY for liraglutide 1.8 mg compared with sitagliptin, and £9851 per QALY for liraglutide 1.2 mg compared with sitagliptin. The ERG conducted additional sensitivity analyses and concluded that the factors that carried most weight were:

- in the comparison with glargine, the direct utility effects of body mass index (BMI) changes and SBP, with some additional contribution from HbA_{1c}
- in the comparison with exenatide, HbA_{1c}, with some additional effects from cholesterol and triglycerides
- in the comparison with sitagliptin, HbA_{1c} and direct utility effects of BMI changes.

The European Medicines Agency has approved liraglutide in dual therapy with other oral glucose-lowering agents. NICE guidance recommends the use of liraglutide 1.2 mg in triple therapy when glycaemic control remains or becomes inadequate with a combination of two oral glucose-lowering drugs. The use of liraglutide 1.2 mg in a dual therapy is indicated only in patients who are intolerant of, or have contraindications to, three oral glucose-lowering drugs. The use of liraglutide 1.8 mg was not approved by NICE. The ERG recommends research into the (currently unlicensed) use of liraglutide in combination with long-acting insulin.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Liraglutide for the treatment of type 2 diabetes*.[2]

Description of the underlying health problem

Type 2 diabetes mellitus is one of the most common chronic metabolic disorders found in both England and Wales. In England, it is estimated that > 2.1 million people have diabetes mellitus and the majority, i.e. about 90% of them, have type 2 diabetes.[3]

Type 2 diabetes is treated first with lifestyle measures aiming at weight loss and increased physical activity, but most patients will need drug treatment as well, partly because most do not achieve sufficient weight loss. However, type 2 diabetes is a progressive disease because of loss over time of beta-cell capacity and falling insulin production. Standard therapy in the UK is to add metformin as first drug when lifestyle measures fail, and then to add a sulphonylurea. When dual therapy fails, triple therapy with insulin or a glitazone is next.[4] However, many patients fail to achieve good control on insulin, and weight gain is a common unwanted side effect.

Scope of the decision problem

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Naturally occurring GLP-1 is released by the small intestine in response to food, and has a number of actions, including stimulating insulin release, inhibiting glucagon release, delaying gastric emptying and promoting a feeling of satiety. Liraglutide is taken once daily and has a plasma half-life of approximately 13 hours (compared with that of native GLP-1, 1.5–2.1 minutes).[5] Liraglutide (Victoza®, Novo Nordisk) received marketing authorisation by the European Medicines Agency on 30 June 2009. It was subsequently launched in the UK on 6 July 2009. Liraglutide is licensed for treatment of adults with type 2 diabetes mellitus in combination with (1) metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea or (2) metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

The Novo Nordisk submission provided data on the clinical effectiveness of liraglutide as a second- and third-line drug for type 2 diabetes, taken from a suite of trials known as the LEAD (Liraglutide Effects and Actions in Diabetes) trials. Two doses are available in the UK: 1.2 or 1.8 mg once daily. The trials compared liraglutide with glargine and exenatide in triple therapy, and with sitagliptin, rosiglitazone and glimepiride in dual therapy.

The annual costs are £954.84 for the 1.2-mg dose and £1432.26 for the 1.8-mg dose.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE. The ERG review was also informed by a Cochrane review[6] of the GLP-1 agonists being undertaken by the Diabetes and Health Technology Assessment group at the University of Aberdeen.

The ERG ran searches to identify studies that compared safety and efficacy of liraglutide with other drugs. To compare data and also to resolve some discrepancies, the ERG used the submission, the published papers and the full clinical trial reports of some trials (LEAD-5,[7] LEAD-6[8] and Pratley and colleagues[9]) provided by the manufacturer.

The Novo Nordisk submission used the Center for Outcomes Research (CORE) model for economic analysis. Although this model is not one of the standard software packages defined by NICE, it was agreed by NICE and the ERG that it would be acceptable because the complexity of

economic modelling in diabetes made it sensible to use an existing and tried-and-tested model rather than develop a new one.

The ERG carried out additional sensitivity analyses using the CORE model.

Results

Summary of submitted clinical evidence

Of the six clinical trials[8–12] included in the submission report, five were published in full and one was then unpublished.[9] All were sponsored by the manufacturer. The main evidence was from the LEAD phase III randomised controlled trials. All trials were multicentred and had glycated haemoglobin (HbA_{1c}) level as the primary outcome. Secondary outcomes measured included percentage of patients reaching HbA_{1c} level of 7%, percentage of patients reaching HbA_{1c} level of < 6.5%, changes in body weight, body mass index (BMI), fasting plasma glucose (FPG), systolic blood pressure (SBP) and lipids, and numbers of patients experiencing adverse events, such as hypoglycaemia and nausea. Patients aged 18–80 years were included and all trials had a duration of 26 weeks.

All studies analysed data for the intention-to-treat population for subjects who were exposed to at least one dose of the drug and had one postbaseline measurement of the parameter. Each end point was analysed using an analysis of covariance model with treatment, pretreatment and country as fixed effects and baseline as a covariate. Missing data were imputed as last observation carried forward.

One of the recommendations in the NICE guideline is that GLP-1 agonists should be used as a triple therapy only in people whose control is unsatisfactory on a combination of two oral agents, usually metformin and a sulphonylurea. Some people would be unable to tolerate these and might take a glitazone or a gliptin instead. Therefore, on the basis of this guideline, not all LEAD trials were relevant. Therefore, the ERG paid most attention to the studies that compared liraglutide in triple therapy, but studies that used liraglutide in dual therapy were reviewed in case NICE decided to approve it for such use.

The two trials that were most relevant were LEAD-5,[7] in which liraglutide 1.8 mg was compared with the long-acting insulin glargine (in combination with metformin and glimepiride), and LEAD-6,[8] in which liraglutide 1.8 mg was compared with another GLP-1 agonist, exenatide. Approximately 63% of patients in both arms were on metformin plus a sulphonylurea, with 27.5% on metformin only and ~9.5% on sulphonylurea only.[8]

In LEAD-5,[7] liraglutide 1.8 mg daily reduced HbA_{1c} level by 0.24% ($p = 0.0015$) more than glargine 24 units/day. Liraglutide also resulted in statistically significant reductions in weight (3.4 kg) and SBP (4.51 mmHg) compared to glargine, but no difference in FPG. The ERG wondered if the dose of glargine had been sufficiently titrated, being only 24 units a day at study end.

In LEAD-6,[8] liraglutide reduced HbA_{1c} level by 0.33% ($p < 0.0001$) more than exenatide twice daily. FPG was reduced by 1.01 mmol/l ($p < 0.0001$) in favour of liraglutide, but weight and SBP showed no significant difference. There was less nausea with liraglutide.

Three trials[9–11] examined liraglutide in dual therapy. LEAD-1[10] compared liraglutide 1.2 and 1.8 mg with rosiglitazone 4 mg daily, added to existing sulphonylurea in both arms. Liraglutide showed a significant improvement in HbA_{1c} level, but no difference in weight and SBP.

LEAD-2[11] investigated patients who were inadequately controlled on metformin alone, and compared liraglutide 1.2 and 1.8 mg daily with glimepiride (a sulphonylurea) as the second drug. There was no difference in HbA_{1c} level between the drugs, but liraglutide showed a favourable difference in weight of 3.7 kg and SBP of 3.2 mmHg compared with glimepiride.

Pratley and colleagues[9] compared the efficacy and safety of liraglutide 1.2 or 1.8 mg once daily with sitagliptin 100 mg once daily. All groups continued on metformin therapy. Compared with sitagliptin, liraglutide 1.2 mg showed a reduction in HbA_{1c} level of 0.34%, a reduction in weight of 1.9 kg and an increase in SBP of 0.39 mmHg.

Because of the significant cost difference between the two doses of liraglutide, the ERG compared the relative benefits between the two in the meta-analyses shown in *Figures 1–4*. Data used in the meta-analyses come from a fully published paper.[9–12] There were no significant differences in changes in HbA_{1c}, in proportions achieving HbA_{1c} level or in SBP. There was a statistically significant difference in weight, of 0.48 kg, where the clinical significance is doubtful.

As the trials were of short duration, there was a lack of data on the long-term safety of liraglutide. Concerns have been raised about the risk of pancreatitis with GLP-1 agonists.

The ERG concluded that liraglutide was effective in lowering blood glucose, while avoiding weight gain and hypoglycaemia, and was a useful addition to the therapeutic options available for type 2 diabetes.

Summary of submitted cost-effectiveness evidence

The manufacturer based cost-effectiveness analysis on data from LEAD-5[7] (liraglutide 1.8 mg vs glargine), LEAD-6[8] (liraglutide 1.8 mg vs glargine) and a trial by Pratley and colleagues[9] (liraglutide 1.2 and 1.8 mg vs sitagliptin). The ERG re-ran the base cases in the CORE model, using the manufacturer's assumptions, and the results matched with those reported in the submission. The measure of health benefits was quality-adjusted life-years (QALYs). The manufacturer estimated the incremental cost-effectiveness ratios to be £15,130 per QALY for liraglutide 1.8 mg compared with glargine, £10,054 per QALY for liraglutide 1.8 mg compared with exenatide, £10,465 per QALY for liraglutide 1.8 mg compared with sitagliptin and £9851 per QALY for liraglutide 1.2 mg compared with sitagliptin. It was also reported that liraglutide was more cost-effective for patients with higher BMI; however, the cost-effectiveness for patients with lower BMI was not reported.

The ERG conducted additional sensitivity analyses and concluded that the factors that carried most weight were:

- in the comparison with glargine, the direct utility effects of BMI changes and SBP, with some additional contribution from HbA_{1c}
- in the comparison with exenatide, HbA_{1c}, with some additional effects from cholesterol and triglycerides
- in the comparison with sitagliptin, HbA_{1c} and direct utility effects of BMI changes.

Because the trials were of short duration, the costs and outcomes in the CORE model had to be modelled far beyond the duration of the trials.

Commentary on the robustness of submitted evidence

The manufacturer gives an accurate description of type 2 diabetes and of the current treatments available, correctly noting that existing treatments are not wholly satisfactory and that patients often suffer from adverse events, such as hypoglycaemia and weight gain. However, the

Study or subgroup	Liraglutide 1.2 mg Mean	SD	Total	Liraglutide 1.8 mg Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
LEAD-1 Marre 2009[10]	−1.08	1.06	228	−1.13	1.07	234	30.4%	0.05 (−0.14 to 0.24)
LEAD-2 Nauck 2009[11]	−1	1.55	240	−1	1.56	242	18.1%	0.00 (−0.28 to 0.28)
LEAD-4 Zinman 2009[12]	−1.5	1.33	178	−1.5	1.33	178	18.3%	0.00 (−0.28 to 0.28)
Pratley 2010[9]	−1.24	1.04	221	−1.5	0.89	218	33.2%	0.26 (0.08 to 0.44)
Total (95% CI)			**867**			**872**	**100.0%**	**0.10 (−0.03 to 0.23)**

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 4.22$, df = 3 ($p = 0.24$); $I^2 = 29\%$
Test for overall effect: $z = 1.50$ ($p = 0.13$)

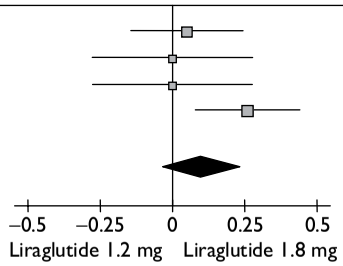

FIGURE 1 Change in HbA_{1c} level (%) from baseline liraglutide 1.2 versus 1.8 mg.

Study or subgroup	Liraglutide 1.2 mg Patients	Total	Liraglutide 1.8 mg Patients	Total	Weight	Risk ratio M-H, Random, 95% CI
LEAD-1 Marre 2009[10]	80	228	98	234	23.6%	0.84 (0.66 to 1.06)
LEAD-2 Nauck 2009[11]	85	240	103	242	24.0%	0.83 (0.66 to 1.04)
LEAD-4 Zinman 2009[12]	102	178	96	178	26.4%	1.06 (0.88 to 1.28)
Pratley 2010[9]	124	221	95	218	26.1%	1.29 (1.06 to 1.56)
Total (95% CI)		**867**		**872**	**100.0%**	**1.00 (0.81 to 1.22)**
Total events	391		392			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 11.92$, df = 3 ($p = 0.008$); $I^2 = 75\%$
Test for overall effect: $z = 0.04$ ($p = 0.97$)

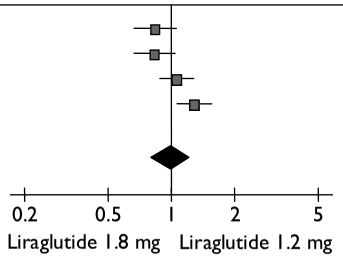

FIGURE 2 Patients reaching HbA_{1c} level of <7% liraglutide 1.2 versus 1.8 mg.

Study or subgroup	Liraglutide 1.2 mg Mean	SD	Total	Liraglutide 1.8 mg Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
LEAD-1 Marre 2009[10]	0.3	3.02	228	−0.2	3.06	234	33.4%	0.50 (−0.05 to 1.05)
LEAD-2 Nauck 2009[11]	−2.6	3.1	240	−2.8	3.11	242	33.4%	0.20 (−0.35 to 0.75)
LEAD-4 Zinman 2009[12]	−1	4	178	−2	4	178	14.9%	1.00 (0.17 to 1.83)
Pratley 2010[9]	−2.86	4.01	221	−3.38	3.99	218	18.3%	0.52 (−0.23 to 1.27)
Total (95% CI)			**867**			**872**	**100.0%**	**0.48 (0.16 to 0.80)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.50$, df = 3 ($p = 0.48$); $I^2 = 0\%$
Test for overall effect: $z = 2.92$ ($p = 0.003$)

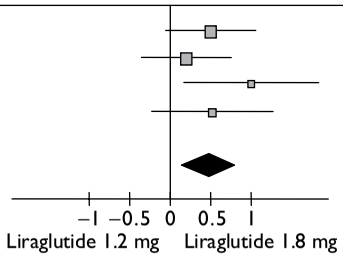

FIGURE 3 Change in weight (kg) from baseline liraglutide 1.2 versus 1.8 mg.

Study or subgroup	Liraglutide 1.2 mg Mean	SD	Total	Liraglutide 1.8 mg Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
LEAD-1 Marre 2009[10]	−2.56	12.83	228	−2.81	13.16	234	28.2%	0.25 (−2.12 to 2.62)
LEAD-2 Nauck 2009[11]	−2.81	13.32	240	−2.29	12.91	242	28.8%	−0.52 (−2.86 to 1.82)
LEAD-4 Zinman 2009[12]	−6.7	14.68	178	−5.6	14.68	178	17.0%	−1.10 (−4.15 to 1.95)
Pratley 2010[9]	−0.55	13.23	221	−0.72	13.14	218	26.0%	0.17 (−2.30 to 2.64)
Total (95% CI)			**867**			**872**	**100.0%**	**−0.22 (−1.48 to 1.04)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.63$, df = 3 ($p = 0.89$); $I^2 = 0\%$
Test for overall effect: $z = 0.35$ ($p = 0.73$)

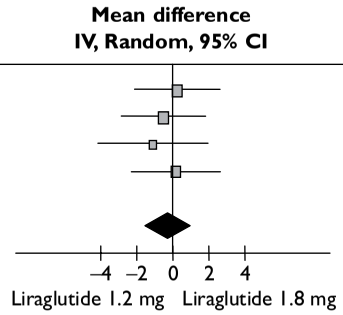

FIGURE 4 Change in SBP (mmHg) from baseline liraglutide 1.2 versus 1.8 mg.

manufacturer did not report the findings of a trial that compared insulin against an intensive lifestyle intervention in patients poorly controlled by combination oral glucose-lowering agents. Aas and colleagues[13] reported that intensive life modification was better than starting insulin. However, the findings of Aas and colleagues[13] were not confirmed in the TULIP (Testing the Usefulness of gLargine when Initiated Promptly) study.[14] The latter,[14] sponsored by the manufacturer of glargine, reported that adding glargine early in the conventional treatment with oral glucose-lowering drugs and lifestyle interventions resulted in better glycaemic control than intensifying lifestyle interventions.

The LEAD studies are of good quality. The trials were conducted in multiple settings in multiple countries, therefore increasing the generalisability of the results, though only a few patients were from the UK.

NICE recommends neutral protamine Hagedorn (NPH) as the first-choice basal insulin in type 2 diabetes, and none of the liraglutide trials provides a comparison with NPH. This might be justified on the grounds that glargine is now the most commonly used long-acting insulin,[15] but NPH is considerably cheaper. The advantages of glargine over NPH in type 2 diabetes are slight.[16]

One weakness was the short durations of the trials. We do not have data on how long the GLP-1 agonists will be effective for in this progressive disease. The ERG and the manufacturer assumed a mean duration of use of 5 years.

Conclusions

The Novo Nordisk submission was considered to be of good quality. All of the relevant studies were included. Evidence from the trials shows that liraglutide is a useful addition to options for treating type 2 diabetes, being effective in reducing blood glucose while avoiding hypoglycaemia and weight gain. The ERG did not think the marginal benefits of the 1.8-mg dose over the 1.2-mg dose justified the much higher cost. Data are required on long-term safety of the drug, as are trials against other options in triple therapy. The ERG noted that trials were under way on use in combination with long-acting insulin, a use that seems logical but which is not currently licensed.

Summary of NICE final guidance issued as a result of the STA

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 ($HbA_{1c} \geq 7.5\%$, or other higher level agreed with the individual), and the person has:

- a BMI of $\geq 35\ kg/m^2$, is of European descent (with appropriate adjustment for other ethnic groups) and has specific psychological or medical problems associated with high body weight, *or*
- a BMI of $< 35\ kg/m^2$, 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 HbA_{1c} 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 HbA_{1c} 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.

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