NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Liraglutide for managing overweight and obesity

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using liraglutide in the NHS in England. The appraisal committee has considered the evidence submitted by the company, the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Is the company's proposed population the population that would benefit most from liraglutide?
- Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using liraglutide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 February 2020

Second appraisal committee meeting: 25 February 2020

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Liraglutide is not recommended, within its marketing authorisation, for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity.

1.2 This recommendation is not intended to affect treatment with liraglutide that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue without changes to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Obesity is very common in England, affecting about 26% of the adult population. Current management for overweight and obesity is lifestyle measures alone, lifestyle measures with orlistat, or bariatric surgery.

Clinical trial evidence shows that liraglutide with lifestyle measures is more effective for weight loss and delaying the development of type 2 diabetes than lifestyle measures alone. But its long-term effectiveness, particularly on the risk of cardiovascular disease, is unknown.

In its submission, the company made a case for liraglutide's cost-effectiveness in people who were considered at high risk of the adverse consequences of obesity, that is, adults with a BMI ≥ 35 kg/m^2 with pre-diabetes and a high risk of cardiovascular disease. It did not provide evidence for the whole population covered by the marketing authorisation.

Because of the uncertainty in the clinical evidence, even in this high-risk subgroup, the cost-effectiveness estimate is highly uncertain and potentially much higher than what NICE considers a cost-effective use of NHS resources. Therefore, liraglutide cannot be recommended.

2 Information about liraglutide

Marketing authorisation indication

2.1 Liraglutide (Saxenda, Novo Nordisk) is indicated 'as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial BMI of ≥30 kg/m² (obese), or ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea'.

Dosage in the marketing authorisation

2.2 The starting dosage is 0.6 mg once daily by subcutaneous injection. The dosage should be increased to 3.0 mg once daily in increments of 0.6 mg with at least 1-week intervals to improve gastro-intestinal tolerability. If escalation to the next dose step is not tolerated for 2 consecutive weeks, consider stopping treatment. Daily doses higher than 3.0 mg are not recommended. Treatment should be stopped after 12 weeks on the 3.0 mg per day dosage if the patient has not lost at least 5% of their initial body weight. For full details of dose schedules, see the summary of product characteristics.

Price

2.3 The list price of liraglutide (Saxenda) is £196.20 for 5 x 6 mg/ml 3-ml (18 mg) pre-filled pens. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Novo Nordisk, a review of this submission by the evidence review group, and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 35), and took these into account in their decision making. It discussed all the issues (1 to 7) which were outstanding after the technical engagement stage.

Clinical need

Living with obesity is restrictive

3.1 The patient expert explained that living with obesity is challenging and restrictive. There is stigma associated with being obese. The biological and psychological determinants of obesity are often overlooked with a general perception that people are obese by choice. Current treatment options are limited and there is a need for a treatment that deals with biological determinants of obesity. The committee understood the need for more treatment options that are effective in managing obesity.

The company submission focused on a 'high-risk' subgroup

3.2 The scope issued by NICE included people with a BMI of 30 kg/m^2 or more (obese), or from 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbidity. This is the population in the marketing authorisation. The company only presented evidence for people with a BMI of 35 kg/m^2 or more, with pre-diabetes and a high risk of cardiovascular disease. The company argued that this group of people was at high risk of experiencing the adverse consequences of obesity and was likely to gain most from liraglutide. The technical team heard at technical engagement that the population proposed by the company was clearly identifiable and justified. However, the evidence presented did not allow the committee to make a recommendation for the full population covered by the marketing authorisation. The committee therefore agreed to focus on the population proposed by the company.

Current management and comparators

Access to tier 3 weight management services varies across England

3.3 The clinical experts explained that weight management follows NICE's clinical guideline on obesity: identification, assessment and management. In the high-risk population proposed by the company, liraglutide would be offered through specialist multidisciplinary weight management (tier 3) services. These provide dietary, lifestyle and behaviour modification, with or without drug therapy, and psychological support. The clinical experts explained that long-term weight loss would not be achieved without the ongoing and psychological support that is a feature of tier 3 services. The committee heard that access to these services varies across England. The clinical experts advised that diabetic services in the NHS have experience with liraglutide prescribing and might provide a suitable alternative where no tier 3 service is available. However, these services may not provide psychological support for weight management. The committee concluded that a tier 3 service is the appropriate context in which liraglutide would be offered but acknowledged that, at present, access to these services is variable.

Orlistat and bariatric surgery would not be alternatives to liraglutide for most people

3.4 The clinical experts explained that many people decide not to have orlistat or stop taking it because of its undesirable side effects. Most people referred to a tier 3 service will have tried and stopped orlistat, so there is a high clinical need for other pharmacological options. The clinical experts explained that liraglutide would only be considered if orlistat or bariatric surgery are not an option for the patient or they do not want to have these treatments. Only around 0.1% of people who are eligible for bariatric surgery have it. The committee concluded that for most people, orlistat and bariatric surgery would not be alternatives to liraglutide and that a

comparison with standard management without pharmacotherapy was appropriate for decision-making.

Clinical evidence

The evidence from a post-hoc subgroup of trial 1839 may not be reliable

3.5 In order to estimate the effectiveness of liraglutide in its proposed population, the company presented a post-hoc subgroup analysis of trial 1839. This trial is a randomised double-blind trial of liraglutide or placebo both used together with diet and exercise. The trial included 3,721 people with and without pre-diabetes. Pre-diabetes was a pre-defined subgroup that included 2,254 people who were followed up for 3 years. The company's post-hoc subgroup came from this pre-defined pre-diabetes subgroup. It included 800 people with a body mass index (BMI) of 35 kg/m^2 or more, with pre-diabetes (defined as a haemoglobin A1c [HbA1c] level of 42 to 47 mmol/mol [6.0 to 6.4%] or a fasting plasma glucose level of 5.5 to 6.9 mmol/L), and a high risk of cardiovascular disease (defined as a total cholesterol level of more than 5 mmol/L, or systolic blood pressure (SBP) of more than 140 mmHg, or a high-density lipoprotein (HDL) level of less than 1.0 mmol/L for men and less than 1.3 mmol/L for women). Weight-related outcomes (BMI and percentage weight loss) significantly favoured liraglutide when compared with placebo. There were significantly fewer confirmed type 2 diabetes cases with liraglutide than with placebo, and more patients became normoglycaemic on liraglutide than on placebo. The committee considered that the trial was of good quality. The post-hoc subgroup population was identifiable, in that it represented a high-risk population of people who were likely to have had a higher absolute benefit from liraglutide. However, the committee had reservations about the use of data from a post-hoc subgroup that would be associated with more uncertainty than the larger pre-defined pre-diabetes trial population.

The evidence for clinical effectiveness should have come from the full pre-defined trial population

3.6 The committee had concerns over the use of post-hoc subgroup data for clinical effectiveness in the company's model. It agreed that the post-hoc subgroup population was appropriate for consideration in that it represented a high-risk population of people who were more likely to get an absolute benefit from liraglutide than people who do not meet the defined criteria. But it was concerned that the post-hoc subgroup may have compromised randomisation. The committee concluded that the relative clinical effectiveness of liraglutide should have been estimated from the whole pre-diabetes population in the trial because this was larger, pre-specified and associated with less uncertainty than the smaller post-hoc subgroup.

Cardiovascular benefits were based on surrogate outcomes and are therefore subject to uncertainty

3.7 The committee considered the evidence from trial 1839, which did not show a significant reduction in cardiovascular outcomes in people having liraglutide compared with placebo. It noted the small number of significant cardiovascular events in the trial. The average age of the population was 48, in whom the baseline cardiovascular risk would not be particularly high. The company had indicated that weight gain stops at around age 67 because of loss of muscle mass, and therefore the average age of patients in the trial was not an unreasonable estimate of those who might be offered liraglutide in clinical practice. The company included a cardiovascular benefit of liraglutide in their model based on cardiovascular risk reduction through surrogate outcomes such as HbA1c and blood pressure. The committee concluded that the estimation of any reduction in cardiovascular events would be subject to uncertainty because they would rely on an estimation of the relationship between the surrogate and the clinical event.

Duration of treatment

Treatment for obesity is likely to be recurrent or continued beyond 2 years

3.8 The committee considered that for long-term conditions, such as hypertension and diabetes, treatment is ongoing. Because obesity is a long-term condition, the committee sought justification for why the company proposed that all patients who have an initial weight loss of more than 5% would stop treatment at 2 years. The clinical experts explained that people who have lost weight are likely to want to continue taking the treatment. This was confirmed by the patient expert. The clinical experts also explained that people who experience side effects with minimal weight loss are most likely to stop taking the treatment. The clinical experts stated that some people would take liraglutide until they achieve their desired weight loss then stop taking it, restarting it when they regain weight. The committee had concerns that the company's submission was based on a maximum treatment duration of 2 years. It noted the clinical experts' comments and concluded that some people might stop treatment before 2 years and then wish to re-start, but others might wish to continue treatment beyond 2 years. The committee acknowledged that a 2-year stopping rule would be implementable in the NHS but noted that it does not reflect what was done in the clinical trial or address the clinical need to reduce weight and then maintain a reduced weight.

Company's economic model

The company's economic model is suitable for decision making

3.9 The company submitted a cohort state-transition model, including 10 health states, to estimate the cost effectiveness of liraglutide compared with diet and exercise. Transitions between health states were based on the estimation of T2DM status, CV events (primary and secondary) using risk models as well as death probabilities. A once-only transition was used to incorporate the proportion of patients reversing from pre-diabetes to

normal glucose tolerance based on Trial 1839 data. The relative treatment effectiveness was estimated through changes in the BMI, SBP, total and HDL cholesterol parameters in the risk models. Patients were assumed to have stopped treatment at 2 years and regain their baseline weight over the next 3 years but not return to the expected higher weight. Patients entered the model with pre-diabetes. The committee considered that the health states and transitions in the model were suitable for decision making but the risk equations to estimate the long-term cardiovascular risk introduced uncertainty

Cardiovascular risk was determined using risk equations

3.10 The company's model used risk equations to estimate the long-term risk of myocardial infarction, angina and stroke (including transient ischaemic attack). The risk equations used surrogate effectiveness parameters such as BMI, SBP, total cholesterol and HDL. The committee considered that the risk equations are not prognostic on an individual basis and are based on an assumption of a steady-state. The committee acknowledged that there was no clear alternative to the use of risk equations in the model, but it had concerns about the assumptions of cardiovascular outcome benefits that were based on temporary improvements in risk factors. The committee was satisfied that liraglutide, when used as proposed by the company, has a temporary benefit on weight and diabetic status. But it required stronger evidence that short-term weight loss and a temporary improvement in diabetic status reduced cardiovascular risk to the extent shown in the model, when there was no clinical trial evidence showing that liraglutide reduces cardiovascular events in the proposed population. It also required a better justification for the surrogate outcomes used to predict long-term benefits in the model. It noted in the company's scenario analyses that if only the effect on BMI was included in the model, the incremental cost-effectiveness ratio (ICER) exceeded £100,000 per quality-adjusted life year (QALY) gained. This was considerably reduced to just under £50,000 per QALY gained if benefits related to the effects on

diabetic status were included. It further reduced to just over £21,000 per QALY gained if additional cardiovascular benefits were included. The committee concluded that it required further explanation and justification of the benefits on cardiovascular events assumed in the economic analysis before it could be persuaded that liraglutide was cost-effective.

The company's assumptions used to predict weight gain and diabetic status were associated with uncertainty

3.11 No follow-up data were available on weight gain and diabetic status after stopping treatment. The company assumed that, after completing a 2-year course of liraglutide, weight would gradually increase over the next 3 years. It also assumed that people who had become normoglycaemic on treatment would have pre-diabetes after 3 years. The committee noted that people in the model regained their initial weight rather than a higher weight, which might be expected for people with untreated obesity. Because no follow-up data were available for weight gain or diabetic status in the 3 years after stopping treatment, the committee accepted that some assumptions had to be made. However, it concluded that the company's assumptions were associated with uncertainty.

The company's model assumes that all people who have a cardiovascular event develop type 2 diabetes

3.12 The committee discussed the company's 'simplifying' assumption that all people who have a cardiovascular event develop type 2 diabetes within the following year. The clinical experts explained that people are more likely to be diagnosed with type 2 diabetes after a cardiovascular event, but this relationship is not causal. The committee heard that there is no good evidence to determine the proportion of people who would develop type 2 diabetes after a cardiovascular event. The committee was concerned that the company's assumption overestimates the clinical and cost effectiveness of liraglutide.

Conclusion

Liraglutide is not recommended

3.13 The committee noted that liraglutide with diet and exercise is an effective short-term treatment for weight loss and has temporary benefits on diabetic status. However, the ICER for liraglutide could as high as £105,000 if only the effects on BMI are included. The committee identified several uncertainties around the modelling assumptions, particularly about what happens after stopping liraglutide and the calculation of long-term benefits. These result in considerable uncertainty about the true ICER. Therefore, the committee was unable to recommend liraglutide as a cost-effective treatment for use in the NHS for adults with a BMI of 35 kg/m^2 or more, with pre-diabetes and a high risk of cardiovascular disease.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
December 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sarah Wood
Technical lead

Rufaro Kausi
Technical adviser

Thomas Feist
Project manager

ISBN: [to be added at publication]