NICE National Institute for Health and Care Excellence

NICE guidance

Liraglutide for managing overweight and obesity

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces ES14.

This guidance should be read in conjunction with PH38.

1 Recommendations

1.1 Liraglutide is recommended as an option for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults, only if:

- they have a body mass index (BMI) of at least 35 kg/m^2 (or at least 32.5 kg/m^2 for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population) and
- they have non-diabetic hyperglycaemia (defined as a haemoglobin A1c level of 42 mmol/mol to 47 mmol/mol [6.0% to 6.4%] or a fasting plasma glucose level of 5.5 mmol/litre to 6.9 mmol/litre) and
- they have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia and
- it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service and
- the company provides it according to the commercial arrangement.

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

Management for overweight and obesity in adults includes lifestyle measures alone, lifestyle measures with orlistat, or bariatric (weight loss) surgery.

The company's evidence submission focuses on people with a BMI of at least 35 kg/m^2 with non-diabetic hyperglycaemia and a high risk of cardiovascular disease, because this group of people was at high risk of experiencing the adverse consequences of obesity. They were also likely to gain most from liraglutide. The clinical evidence shows that people lose more weight with liraglutide plus lifestyle measures than with lifestyle measures alone. Liraglutide has also been shown to delay the development of type 2 diabetes and cardiovascular disease.

People from some minority ethnic groups are at an equivalent risk of the consequences of obesity at a lower BMI than the white population. NICE's guideline on BMI recommends using lower BMI thresholds for people from south Asian, Chinese, black African and African-Caribbean populations when identifying the risk of developing type 2 diabetes and providing interventions to prevent it. Therefore, a similar adjustment in the BMI threshold is appropriate when considering liraglutide for people from minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.

For people with a high BMI, non-diabetic hyperglycaemia and a high risk of cardiovascular disease the cost-effectiveness estimates are within what is normally considered a cost-effective use of NHS resources. For these people, liraglutide is recommended.

2 Information about liraglutide

Marketing authorisation

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 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 × 6 mg/ml 3-ml (18 mg) pre-filled pens (excluding VAT; BNF online, accessed September 2020). The company has a commercial arrangement. This makes the Saxenda brand of liraglutide available to the NHS with a discount only if it is purchased through a secondary-care tier 3 weight management service. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Novo Nordisk, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal 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 its decision making. It discussed the following issues (issues 1 to 7) that 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 need for a treatment that deals with biological determinants of obesity. The committee recognised there are limited effective treatment options available for people living with obesity.

The company submission focuses on a high-risk subgroup

3.2 The NICE scope included people with a body mass index (BMI) of 30 kg/m^2 or more (obese), or with a BMI 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 (non-diabetic hyperglycaemia) and a high risk of cardiovascular disease. It stated that these people are at high risk of experiencing the adverse consequences of obesity and are likely to gain the most from liraglutide. It was agreed 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

3.3 The clinical experts explained that weight management follows NICE's guideline on identification, assessment and management of obesity. 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. Access to these services varies across England. The clinical experts advised that NHS diabetic services have experience of prescribing liraglutide and might provide a suitable alternative when 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 varies.

Orlistat and bariatric surgery are not 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 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 orlistat and bariatric surgery would not be alternatives to liraglutide for most people, and that the appropriate comparator is lifestyle changes without medicines.

Clinical evidence

The company's modified intention-to-treat analysis is suitable for decision making

3.5 The company presented a post-hoc subgroup analysis of trial 1839. This is a randomised double-blind trial of liraglutide or placebo, alongside diet and exercise. It included 3,721 people with and without pre-diabetes (non-diabetic hyperglycaemia). Pre-diabetes was a pre-defined subgroup of 2,254 people who were followed up for 3 years. The post-hoc subgroup came from this pre-defined pre-diabetes subgroup. It included 800 people with a BMI of 35 kg/m^2 or more, with pre-diabetes (defined as a haemoglobin A1c level of 42 mmol/mol to 47 mmol/mol [6.0% to 6.4%] or a fasting plasma glucose level of 5.5 mmol/litre to 6.9 mmol/litre), and a high risk of cardiovascular disease (defined as the presence of 1 or more of: a total cholesterol level of more than 5 mmol/litre, systolic blood pressure of more than 140 mmHg, or a high-density lipoprotein level of less than 1.0 mmol/litre for men and less than 1.3 mmol/litre for women). Weight-related outcomes (BMI and percentage weight loss) significantly favoured liraglutide compared with placebo. Statistically significantly fewer people developed type 2 diabetes with liraglutide than with placebo, and more patients reverted to normal glucose tolerance 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 a higher absolute benefit from liraglutide. The committee noted that the post-hoc subgroup is associated with more uncertainty than the larger pre-defined pre-diabetes trial population. The company explained that its modified intention-to-treat analysis included efficacy data for the full pre-diabetes population. The committee concluded that this analysis was suitable for decision making.

The cardiovascular benefits of liraglutide are uncertain

3.6 The committee considered the evidence from the full population of trial 1839, which did not show a significant reduction in cardiovascular events in people having liraglutide compared with placebo over the 3 years of the trial. 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 indicated that weight gain stops 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 cardiovascular benefit of liraglutide in the company's model was based on risk reduction using surrogate outcomes such as haemoglobin A1c and blood pressure. This approach introduces uncertainty because causal inference requires direct evidence that liraglutide reduces cardiovascular events. This was not provided in the company submission because of lack of long-term evidence. The clinical experts explained that reductions in the surrogate outcomes were likely to reduce long-term cardiovascular risk. The committee accepted the clinical experts' opinion that temporary reductions in weight can result in long-term cardiovascular benefits. The committee acknowledged that relying on surrogates is uncertain but accepted that surrogate outcomes were the only available evidence to estimate cardiovascular benefits.

Duration of treatment

Obesity is a long-term condition, therefore limiting treatment to 2 years is not ideal

3.7 The committee noted that obesity is a long-term condition. For other long-term conditions, such as hypertension and diabetes, treatment continues long term. The committee sought justification for the company's proposal that all patients who had an initial weight loss of more than 5% (and so continued on treatment), 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. They stated that some people 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 that a 2-year treatment duration does not address the clinical need to reduce weight and then maintain a reduced weight. Also, it does not reflect the clinical trial. The clinical experts explained that patients are usually discharged from NHS tier 3 weight management services after 2 years of continuous treatment. The committee concluded that treating a chronic condition such as obesity for only 2 years is not ideal. But it accepted that the cost-effectiveness estimate was based on a single course of treatment of no longer than 2 years, and that the assumption that treatment would be stopped at 2 years was reasonable in the context of NHS tier 3 weight management services.

The company's economic model

The health states and transitions in the model are suitable for decision making

3.8 The company submitted a cohort state-transition model with 10 health states, to estimate the cost effectiveness of liraglutide compared with diet and exercise alone. Transitions between health states were based on estimated type 2 diabetes mellitus status and cardiovascular events (primary and secondary). The model used risk equations and 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 BMI, systolic blood pressure, total and high-density lipoprotein cholesterol parameters in the risk models. Patients were assumed to have stopped treatment at 2 years and gain weight over the next 3 years, so they return to the weight expected if they had never had treatment. Patients entered the model with pre-diabetes. The committee noted that the risk equations used relative effectiveness on surrogate end points to estimate long-term

cardiovascular events, which introduced uncertainty. But it concluded that the health states and transitions in the model were suitable for decision making.

The cardiovascular risk equations are suitable for decision making

3.9 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, systolic blood pressure, total cholesterol and high-density lipoprotein. The committee considered that the risk equations were not prognostic on an individual basis and were 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 clinical experts explained that short-term weight loss and temporary improvement in diabetic status can reduce long-term cardiovascular risk. The committee was satisfied that liraglutide, when used as proposed by the company, has a temporary benefit on weight and diabetic status and this could reduce the long-term risk of myocardial infarction, angina and stroke. The company's model included several different risk equations to predict prevention of cardiovascular events, and different risk equations were used in the company's and the ERG's preferred base-case analyses. The committee accepted that the risk equations selected in the company's and ERG's base case were both suitable for decision making.

The assumptions for weight gain and diabetic status are uncertain

3.10 No follow-up data were available on weight gain and diabetic status after stopping treatment in trial 1839. 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 whose glucose tolerance became normal on treatment would revert to being pre-diabetic after 3 years. The committee noted that people in the model regained their initial weight. But they might be expected to regain more

weight after treatment stopped, resulting in a higher weight than before starting treatment. Because no follow-up data were available for weight gain or diabetic status in the 3 years after stopping treatment, the committee accepted the assumptions and the associated uncertainty.

The model assumes that all people develop type 2 diabetes after a cardiovascular event

3.11 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 develop type 2 diabetes after a cardiovascular event. During technical engagement, the company presented a scenario analysis in which people did not develop type 2 diabetes after a cardiovascular event. The committee had reservations about the simplifying assumption but was reassured by the results of the company's scenario analysis. The committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) would be between the base-case ICERs, which applied the simplifying assumption, and the scenario analysis that did not. The ICER is therefore likely to be within what NICE normally considers a cost-effective use of NHS resources.

Cost-effectiveness results

Because of the uncertainty an acceptable ICER is £20,000 per QALY gained

3.12 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. Because of the uncertainties in the modelling assumptions, particularly what happens after stopping liraglutide and the calculation of long-term benefits, the committee agreed that an

acceptable ICER would not be higher than £20,000 per QALY gained.

The company's base-case ICER is below £20,000 per QALY gained

3.13 The company's base-case analysis:

- included clinical-effectiveness estimates from the post-hoc subgroup of trial 1839 (see section 3.5)
- implemented the 2-year treatment duration rule (see section 3.7)
- used the UKPDS-82 risk equation to model primary and secondary cardiovascular disease outcomes (see section 3.9)
- assumed that any weight loss returned to the base weight 3 years after treatment discontinuation (see section 3.10)
- assumed that type 2 diabetes developed in the first year after a cardiovascular event (see section 3.11).

The company's base-case ICER for liraglutide plus diet and exercise compared with diet and exercise alone was £11,293 per QALY gained.

The ERG's base-case ICER is below £20,000 per QALY gained

3.14 The ERG's preferred base-case analysis was similar to the company's base case but included:

- the Qrisk-3 risk equation to predict development of primary cardiovascular disease outcomes (see section 3.9)
- the Framingham recurring coronary heart disease risk equation to predict development of secondary cardiovascular disease outcomes (see section 3.9).

The ERG's preferred base-case ICER for liraglutide plus diet and exercise compared with diet and exercise alone was £13,569 per QALY gained.

All the scenario analyses result in ICERs below £20,000 per QALY gained

3.15 The company's and the ERG's scenario analyses all resulted in an ICER below £20,000 per QALY gained. The committee agreed that the scenario analyses addressed several areas of uncertainty in the economic model. Specifically, the committee noted that:

- the scenario using efficacy data from the whole pre-diabetes population rather than the post-hoc sub group (see section 3.5) reduced the base-case ICER
- removing the assumption that type 2 diabetes always develops after a cardiovascular event (see section 3.11) did not increase the ICER above £20,000 per QALY gained in the company's or the ERG's scenarios.

Other factors

3.16 The committee noted that people from some minority ethnic groups are at an equivalent risk of the consequences of obesity at a lower BMI than the white population. NICE's guideline on BMI recommends using lower BMI thresholds for south Asian, Chinese, black African and African-Caribbean populations when identifying the risk of developing type 2 diabetes and providing interventions to prevent it. The committee agreed that a similar adjustment is appropriate when considering liraglutide. It concluded that the BMI threshold of at least 35 kg/m^2 should be adjusted appropriately when considering liraglutide for people from minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.

Conclusion

Liraglutide is a cost-effective use of NHS resources

3.17 The committee noted that the company's and the ERG's base case and scenario analyses resulted in ICERs for liraglutide of less than £20,000 per QALY gained. The committee therefore recommended liraglutide as a cost-effective treatment for use in the NHS for adults with a BMI of at

least 35 kg/m^2, non-diabetic hyperglycaemia, and a high risk of cardiovascular disease alongside a reduced-calorie diet and increased physical activity. The BMI threshold should be adjusted appropriately for people from minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient is living with obesity and the doctor responsible for their care thinks that liraglutide is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

Richard Mattock and Sarah Wood
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