NICE advice

Obese, overweight with risk factors: liraglutide (Saxenda)

Evidence summary
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Key points

The content of this evidence summary was up-to-date in June 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: New medicine. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Liraglutide (Saxenda) received a European marketing authorisation in March 2015 and was launched in the UK in January 2017. It is licensed 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 or more (obese), or
- from 27 kg/m² to less than 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if patients have not lost at least 5% of their initial body weight.

Liraglutide (Saxenda) is a different licensed product to liraglutide (Victoza) and the doses of liraglutide (Saxenda) used for weight management are different to that used in managing type 2 diabetes (Victoza). Liraglutide (Victoza) has been licensed in the UK for the treatment of type 2

diabetes in adults since 2009. Victoza is not licensed as a pharmacological treatment option for weight management and it also has a different licensed dose range.

Overview

This evidence summary discusses 4 randomised controlled trials (RCTs) in adults who were obese or overweight (BMI 27 kg/m² or above) with a variety of weight-related co-morbidities including dyslipidaemia, hypertension, type 2 diabetes and obstructive sleep apnoea. All of these studies compared liraglutide 3.0 mg daily with placebo and all participants also received lifestyle interventions for weight loss. There are currently no published double blind RCTs which compare liraglutide with other medicines for weight management.

The main efficacy outcomes from the 4 studies included weight loss outcomes, time to onset of type 2 diabetes and change in apnoea-hypopnea index (AHI: apnoea-hypopnea events per hour of sleep). After 32 to 160 weeks' treatment, there was a statistically significant increased weight loss with liraglutide 3.0 mg daily compared with placebo in all 4 studies (an estimated treatment difference of −5.4% to −4.0% in percentage body weight change from baseline across the 4 studies). However, many participants regained weight after stopping treatment. In 1 study in adults without type 2 diabetes, after 56 weeks' treatment with liraglutide, participants who switched to placebo gained 2.91% bodyweight over the following 12 weeks compared with 0.69% for those who continued on liraglutide.

In 1 study in adults with prediabetes, 2% of participants in the liraglutide group developed type 2 diabetes over a 160-week treatment period compared with 6% in the placebo group. There was a reduction in the AHI with liraglutide compared with placebo in 1 study in people with obstructive sleep apnoea. However, the clinical significance of this is unclear as there is no established minimum clinically significant difference for this measure.

The European Public Assessment Report (EPAR) for liraglutide (Saxenda) reports that the general adverse event profile is in-line with that for liraglutide (Victoza). The EPAR states that there is currently insufficient data to assess if uncommon events (pancreatitis/neoplasms) occur more frequently with liraglutide 3.0 mg daily compared with liraglutide 1.8 mg daily. Liraglutide has been associated with an increase in pulse rate, which the EPAR states does not appear to be dose-related.

The NICE guideline on identifying, assessing and managing obesity (2014) recommends considering pharmacological treatment for people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes. The guideline recommends

orlistat as a pharmacological treatment option only as part of a weight management plan in adults who are obese or have a BMI of 28 kg/m^2 or more with associated risk factors, such as type 2 diabetes. Liraglutide (Saxenda) is not specifically mentioned in the NICE guideline, however it is another potential pharmacological treatment option for use in-line with its marketing authorisation, for adults for whom lifestyle and behavioural approaches have not been effective and for whom the potential benefits of treatment outweigh the risks. However, as reported in the EPAR for liraglutide (Saxenda) it is unlikely that any potential weight loss achieved with liraglutide would be sustained after treatment is stopped. The summary of product characteristics (SPC) for liraglutide (Saxenda) does not provide further information on how long treatment should be continued for in people who have lost at least 5% of their initial body weight after 12 weeks treatment. There were high dropout rates in all of the studies so continuation with treatment may be a problem in practice.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- In obese or overweight adults without type 2 diabetes, there was a mean change in body weight from baseline of −8.0% with liraglutide 3.0 mg daily (recommended maintenance dose) and −2.6% with placebo (estimated treatment difference:−5.4%, 95% confidence interval [CI] −5.8% to −5.0%, p<0.001). There was also a statistically significant higher percentage of participants in the liraglutide group who lost 5% or more and 10% or more bodyweight from baseline compared with placebo:
  - 63.2% versus 27.1% (odds ratio [OR] 4.8, 95% CI 4.1 to 5.6, p<0.001) for 5% or more and
  - 33.1% versus 10.6% (OR 4.3, 95% CI 3.5 to 5.3, p<0.001) for 10% or more (Pi-Sunyer et al. 2015, RCT, n=3,731, 56 weeks).
- In obese or overweight adults with type 2 diabetes, there was an estimated mean change in body weight from baseline of −6.0% with liraglutide 3.0 mg daily and −2.0% with placebo (estimated treatment difference:−4.0%, 95% CI −5.1% to −2.9%, p<0.001). There was also a statistically significant higher percentage of participants who lost 5% or more and 10% or more bodyweight from baseline compared with placebo:
  - 54.3% versus 21.4% (estimated treatment difference 32.9%, 95% CI 24.6% to 41.2%, p<0.001) for 5% or more and
  - 25.2% versus 6.7% (estimated treatment difference 18.5%; 95% CI 12.7% to 24.4%, p<0.001) for 10% or more (Davies et al. 2015, RCT, n=846, 56 weeks).
- In obese or overweight adults with prediabetes, 2% of participants in the liraglutide 3.0 mg daily group developed type 2 diabetes compared with 6% in the placebo group (hazard ratio 0.21, 95% CI 0.13 to 0.34, p<0.0001) [le Roux et al. 2017, RCT, n=2,254, 160 weeks].
- In obese adults with obstructive sleep apnoea and a baseline AHI of 49.0 in the liraglutide group and 49.3 in the placebo group, there was a mean reduction in AHI of −12.2 events per hour of sleep in the liraglutide group compared with −6.1 events per hour of sleep in the placebo group (estimated treatment difference: −6.1, 95% CI −11.0 to −1.2, p=0.015) [Blackman et al. 2016, RCT, n=359, 32 weeks].

Safety

- There are several special warnings and precautions for use in the SPC for liraglutide (Saxenda), including warnings on pancreatitis, cholelithiasis and cholecystitis, thyroid disease, heart rate, dehydration and hypoglycaemia in people with type 2 diabetes.
- In the study in overweight adults with type 2 diabetes there were 5 severe hypoglycaemic events in 3 participants in the liraglutide 3.0 mg daily group, 3 events in 2 participants in the liraglutide 1.8 mg daily group compared with no events in the placebo group. All of these severe hypoglycaemic events occurred in participants who were taking concomitant sulfonylureas (Davies et al. 2015, RCT, n=846, 56 weeks).

Patient factors

- Liraglutide is given by subcutaneous injection. Orlistat is an oral treatment, which may be preferable to some patients. Orlistat and liraglutide have different adverse effect profiles, which also need to be considered.
- More participants in the liraglutide 3.0 mg groups withdrew from the studies due to adverse events compared with the placebo groups (from 9.2% to 13.0% with liraglutide 3.0 mg compared with 3.3% to 6.0% with placebo across the 4 studies discussed in the evidence summary).
- Gastrointestinal disorders were the most common adverse events reported in the studies. Across the studies in the clinical development programme, nausea was reported in 39.3% of participants taking liraglutide 3.0 mg daily compared with 13.8% taking placebo (EPAR: Saxenda).

Resource implications

- Liraglutide (Saxenda) costs £196.20 for 30 days' supply at the maintenance dose of 3.0 mg daily (MIMS, May 2017, excluding VAT).
- Orlistat 120 mg 3 times a day costs £18.05 for 30 days' supply (Drug Tariff, May 2017, excluding VAT).
- The manufacturer has reported that they will only promote the use of liraglutide (Saxenda) on private prescription, so they anticipate that use on the NHS will be limited. This evidence summary does not contain recommendations from NICE on whether the medicine should be prescribed within the NHS or by private prescription.

Introduction and current guidance

Obesity is directly linked to a number of different illnesses including type 2 diabetes, fatty liver disease, hypertension, gallstones and gastro-oesophageal reflux disease, as well as psychological and psychiatric morbidities. The NICE guideline on identifying, assessing and managing obesity classifies adults with a BMI over 30 kg/m^2 as obese and those with a BMI of 25 to 29.9 kg/m^2 as overweight. Obesity is a complex problem. Treatment involves multicomponent interventions such as weight management programmes including behaviour change strategies to: increase people's physical activity levels or decrease inactivity, improve eating behaviour and the quality of the person's diet, and to reduce energy intake.

The NICE guideline on identifying, assessing and managing obesity recommends considering pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated. The guideline recommends to consider medicines for people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes. The guideline recommends orlistat as a pharmacological treatment option only as part of a weight management plan in adults who are obese or have a BMI of 28 kg/m^2 or more with associated risk factors, such as type 2 diabetes. Orlistat therapy should be continued beyond 3 months only if the person has lost at least 5% of their initial body weight since starting drug treatment. Rates of weight loss may be slower in people with type 2 diabetes, so less strict goals than those for people without diabetes may be appropriate.

A NICE interactive flowchart on obesity brings together all related NICE guidance and associated products on this topic in a set of interactive topic-based diagrams.

Product overview

Mode of action

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear (summary of product characteristics [SPC]: Saxenda).

Regulatory status

Liraglutide (SPC: Saxenda) is licensed as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of:

- 30 kg/m² or more (obese), or
- from 27 kg/m² to less than 30 kg/m² (overweight) in the presence of at least 1 weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if people have not lost at least 5% of their initial body weight.

Liraglutide (Saxenda) is a different licensed product to liraglutide (Victoza) and the doses of liraglutide (Saxenda) used for weight management are different to that used in managing type 2 diabetes (Victoza). Liraglutide (Victoza) has been licensed in the UK for the treatment of type 2 diabetes in adults since 2009. Victoza is not licensed as a pharmacological treatment for weight management and it also has a different licensed dose range (with a maintenance dose of 1.2 mg to 1.8 mg daily).

Dosing information

One pre-filled Saxenda pen contains 18 mg liraglutide in 3 ml, delivering doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg. The starting dose is 0.6 mg daily and the maintenance dose is 3.0 mg daily. The dose should be increased to 3.0 mg 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, discontinuation of treatment should be considered. Daily doses higher than 3.0 mg are not recommended (SPC: Saxenda).

Cost

Liraglutide18 mg/3 ml solution for injection costs £196.20 for 5 prefilled pens (MIMS, May 2017). The 5 prefilled pens equate to 30 days' supply at the maintenance dose of 3.0 mg daily.

Evidence review

A literature search was conducted which identified 814 references (see search strategy for full details). These references were screened using their titles and abstracts and 9 references were obtained and assessed for relevance.

Four RCTs identified from the search (Pi-Sunyer et al. 2015, le Roux et al. 2017, Davies et al. 2015 and Blackman et al. 2016) were included in this evidence summary. A summary of the included studies is shown in table 2 (see evidence tables for full details).

The European Public Assessment Report (EPAR) for liraglutide (Saxenda) states that the clinical development programme included 4 phase III randomised controlled trials (RCTs) in obese or overweight people with or without diabetes and a phase II dose-finding study. Three of the phase III RCTs have been included in this evidence summary (Pi-Sunyer et al. 2015, Davies et al. 2015 and Blackman et al. 2016). The fourth phase III RCT (in people who had already lost at least 5% of their initial body weight on a low calorie diet) and the dose finding study, which were included in the 9 references obtained and assessed for relevance, were excluded (see excluded studies for details).

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Pi-Sunyer et al. 2015 RCT	Adults (78% female) with either a BMI of 30 kg/m² or above or 27 kg/m² or above in addition to dyslipidaemia or hypertension (n=3,731)	Liraglutide 3.0 mg daily vs. placebo	Co-primary outcomes: • weight change from baseline • proportion of participants who lost at least 5% of their baseline bodyweight • proportion of participants who lost more than 10% of their baseline bodyweight A fourth co-primary outcome of the study on time to onset of type 2 diabetes is assessed in le Roux et al. 2017.

le Roux et al. 2017 RCT	Adults with prediabetes at baseline in Pi-Sunyer et al. 2015 (n=2,254)	Liraglutide 3.0 mg daily vs. placebo	Primary outcome: time to onset of type 2 diabetes
Davies et al. 2015 RCT	Adults (50% female) with type 2 diabetes and a BMI of 27 kg/m² or above (n=846)	Liraglutide 1.8 mg or 3.0 mg daily vs. placebo (the 1.8 mg dose is not licensed for weight management and the results from this arm are not discussed in this evidence summary)	Co-primary outcomes: • weight change from baseline • proportion of participants who lost at least 5% of their baseline bodyweight • proportion of participants who lost more than 10% of their baseline bodyweight
Blackman et al. 2016 RCT	Adults (72% male) with moderate or severe obstructive sleep apnoea and a BMI of 30 kg/m² or above (n=359)	Liraglutide 3.0 mg daily vs. placebo	Change in AHI from baseline
Abbreviations: AHI, apnoea-hypopnea index			

The remaining 5 references were excluded. These are listed in excluded studies with reasons for their exclusion.

Clinical effectiveness

The EPAR for liraglutide (Saxenda) states that the clinical development programme included 4 phase III RCTs in obese or overweight people with or without diabetes and a phase II dose-finding study. Three of the phase III RCTs have been included in this evidence summary (Pi-Sunyer et al. 2015, Davies et al. 2015 and Blackman et al. 2016), in addition to a fourth RCT (le Roux et al. 2017),

an extension of Pi-Sunyer et al. 2015. All of the included studies compared liraglutide 3.0 mg daily with placebo. Davies et al. 2015 included a liraglutide 1.8 mg daily group but the results from that group are not discussed in this evidence summary because that dose is not licensed for this indication.

Weight loss outcomes

Pi-Sunyer et al. 2015 and Davies et al. 2015 both had weight loss primary outcomes; le Roux et al. 2017 and Blackman et al. 2016 had weight loss secondary outcomes. There was a statistically significant weight loss with liraglutide 3.0 mg daily compared with placebo in all 4 studies (an estimated treatment difference of −5.4% to −4.0% in percentage body weight change from baseline across the 4 studies). The EPAR for liraglutide (Saxenda) states that relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10 % of initial body weight. Demonstration of a significant degree of weight loss of at least 10 % of baseline weight which is also statistically greater than that associated with placebo is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity medicines. The NICE guideline on identifying, assessing and managing obesity recommends that orlistat should only be continued beyond 3 months if people have lost at least 5% of their initial body weight since starting treatment (although less strict goals may be appropriate in people with type 2 diabetes).

In Pi-Sunyer et al. 2015 after 56 weeks' treatment, the mean change in body weight from baseline was −8.0% in the liraglutide group and −2.6% in the placebo group with an estimated treatment difference of −5.4% (95% confidence interval [CI] −5.8% to −5.0%, p<0.001). There was a statistically significant higher percentage of participants who lost 5% or more body weight from baseline with liraglutide compared with placebo (63.2% versus 27.1%; difference 36.1%; odds ratio [OR] 4.8, 95% CI 4.1 to 5.6, p<0.001) and who lost more than 10% body weight from baseline (33.1% compared with 10.6%; difference 22.5%; OR 4.3, 95% CI 3.5 to 5.3, p<0.001).

Davies et al. 2015 comprised a population with type 2 diabetes, who were not taking a GLP-1 receptor agonist or insulin at baseline (around 11% treated with diet and exercise alone and around 56% treated with metformin alone). After 56 weeks' treatment, the estimated mean change in body weight from baseline was −6.0% in the liraglutide group and −2.0% in the placebo group with an estimated treatment difference of −4.0% (95% CI −5.1% to −2.9%, p<0.001). There was a statistically significant higher percentage of participants who lost 5% or more body weight from baseline with liraglutide compared with placebo (54.3% compared with 21.4%; estimated treatment difference 32.9%; 95% CI 24.6% to 41.2%, p<0.001) and who lost more than 10% body weight from baseline (25.2% versus 6.7%; estimated treatment difference 18.5%; 95% CI 12.7% to 24.4%, p<0.001).

After 160 weeks' treatment in a population with prediabetes (le Roux et al. 2017), the mean change in body weight from baseline was −6.1% in the liraglutide group and −1.9% in the placebo group with an estimated treatment difference of −4.3% (95% CI −4.9% to −3.7%, p<0.0001). In Blackman et al. 2016, in a population with sleep apnoea, after 32 weeks' treatment the mean change in body weight from baseline was −5.7% in the liraglutide group and −1.6% in the placebo group with an estimated treatment difference of −4.2% (95% CI −5.2% to −3.1%, p<0.0001).

The EPAR for liraglutide (Saxenda) reported that across the clinical trial programme the treatment effect of liraglutide versus placebo for mean body weight change from baseline was −5.2% (5.3 kg). However, there was a high dropout rate in the studies and some of the studies used a last observation carried forward (LOCF) method for missing data (see evidence strengths and limitations). Using a more conservative method for missing data (baseline observation carried forward), the EPAR estimates a treatment effect of −4.28%. The EPAR reported that the efficacy of liraglutide was lower in men; across the clinical study programme the treatment effect for mean body weight change from baseline for women (n=3,759) was −5.83% and the treatment effect for men (n=1,488) was −3.56%.

The EPAR reported that it is not clear if and how long the benefits of liraglutide will persist after treatment discontinuation and that it is likely that weight would return to baseline measures. In Pi-Sunyer et al. 2015, after 56 weeks, participants in the liraglutide group who did not have prediabetes at screening were randomly assigned to continue receiving liraglutide or to switch to placebo for 12 weeks. Participants who switched from liraglutide to placebo gained a mean of 2.91% bodyweight between weeks 56 and 68 compared with 0.69% for those participants who continued on liraglutide.

Additional outcomes

In le Roux et al. 2017, the primary outcome was time to onset of type 2 diabetes in a population of participants with prediabetes (see evidence tables for definition of prediabetes and definition of how type 2 diabetes was diagnosed). Over the 160−week treatment period, 2% of participants in the liraglutide 3.0 mg daily group developed type 2 diabetes compared with 6% in the placebo group (hazard ratio 0.21, 95% CI 0.13 to 0.34, p<0.0001).

In Blackman et al. 2016, the primary outcome was change in the apnoea-hypopnea index (AHI: apnoea or hypopnea events per hour of sleep) from baseline. From a baseline AHI of 49.0 events per hour in the liraglutide 3.0 mg daily group and 49.3 in the placebo group, there was a mean reduction of −12.2 in the liraglutide group and −6.1 in the placebo group after 32 weeks' treatment (estimated treatment difference −6.1 events per hour, 95% CI −11.0 to −1.2, p=0.015). The clinical

significance of this difference is unclear; the EPAR reported that the interpretation of the sleep apnoea related outcomes is difficult because there is no established margin for clinical relevance.

In Pi-Sunyer et al. 2015, there were statistically significant changes from baseline with liraglutide compared with placebo for secondary outcomes including change in waist circumference, BMI, change in systolic blood pressure and change in a fasting total cholesterol (see results tables for details).

An overview of the results for clinical effectiveness can be found in results tables.

Safety and tolerability

There are several special warnings and precautions for use in the summary of product characteristics (SPC) for liraglutide (Saxenda). The SPC includes warnings on pancreatitis, cholelithiasis and cholecystitis, thyroid disease, heart rate, dehydration and hypoglycaemia in people with type 2 diabetes. The SPC recommends that a reduction in the dose of concomitant insulin or sulfonylurea should be considered when liraglutide (Saxenda) is initiated to reduce the risk of hypoglycaemia. The SPC reports a number of patient groups for whom the safety and efficacy of liraglutide for weight management has not been established and it states that use in these patient groups is not recommended. This includes people aged 75 years and older, people with severe renal impairment, people with severe hepatic impairment, people with congestive heart failure class III to IV and people with obesity secondary to endocrine or eating disorders or obesity caused by another medicinal treatment. The SPC also recommends that liraglutide is not recommended for use in people with inflammatory bowel disease and diabetic gastroparesis. See the liraglutide (Saxenda) SPC for further details.

The following are reported as very common (1 in 10 or more) adverse reactions in the liraglutide (Saxenda) SPC: nausea, vomiting, diarrhoea and constipation. Common adverse reactions (from 1 in 100 to 1 in 10) reported in the SPC include hypoglycaemia, insomnia, dizziness, dysgeusia, dry mouth, dyspepsia, gastritis, gastro-oesophageal reflux disease, flatulence, eructation, upper abdomen pain, abdomen distension, cholelithiasis, injection site reactions, asthenia, fatigue, increased lipase and increased amylase.

The EPAR for liraglutide (Saxenda) reported that the general adverse event profile is in-line with that for liraglutide (Victoza) for type 2 diabetes. The safety database that was considered in the EPAR for Saxenda included 5,813 people, with 2,341 people taking the 3.0 mg dose for at least 1 year. The most commonly reported adverse events were gastrointestinal disorders. These included nausea, diarrhoea, constipation and vomiting (reported respectively in 39.3%, 20.9%,

19.4% and 15.7% of participants taking liraglutide 3.0 mg compared with 13.8%, 9.9%, 8.5% and 3.9% of participants taking placebo).

In people without type 2 diabetes, no severe hypoglycaemic events were reported. In people with type 2 diabetes severe hypoglycaemia was reported by 0.7% of people treated with liraglutide 3.0 mg and 1% of people treated with liraglutide 1.8 mg and occurred only in people taking concomitant sulfonylureas. The EPAR stated that injection site reactions were reported more frequently with liraglutide than placebo (13.9% compared with 10.5%). The EPAR further comments that this incidence rate was higher than that reported in completed studies with liraglutide (Victoza) for type 2 diabetes (which was 2.9% for liraglutide (Victoza) compared with 1.5% for comparator).

Overall, the EPAR concluded that the higher liraglutide (Saxenda) dose did not appear to increase adverse event rates compared with the lower liraglutide (Victoza) dose, apart from gastrointestinal disorders which were more frequent. The EPAR stated, however, that there is currently insufficient data to assess if uncommon events (pancreatitis/neoplasms) occur more frequently with liraglutide 3.0 mg daily compared with liraglutide 1.8 mg daily. In addition, the EPAR reported that gallbladder adverse events occurred more frequently with liraglutide 3.0 mg daily compared to 1.8 mg daily. The EPAR stated that the increase in pulse rate associated with liraglutide does not appear to be dose-related.

In Pi-Sunyer et al. 2015, the most common adverse events were gastrointestinal disorders. However, 94% or more were classed as mild or moderate in severity. Gastrointestinal adverse events were the most common reason that participants in the liraglutide group withdrew from the study (6.4% [159/2,481] with liraglutide compared with 0.7% [9/1,242] with placebo). Nausea and vomiting occurred most frequently within the first 4 to 8 weeks after starting treatment with liraglutide. The change in mean resting pulse (beats per min) from baseline was greater in the liraglutide group compared with the placebo group (statistically significant), estimated treatment difference: 2.4 beats per min (95 CI 1.9 to 3.0, $p<0.001$).

Gallbladder adverse events were more common in the liraglutide group than the placebo group (2.5% [61/2481] compared with 1.0% [12/1242]). There were 11 confirmed cases of pancreatitis that occurred during the study and follow-up period, 10 occurred in 2,481 participants in the liraglutide group (0.4%, 0.4 events per 100 patient-years at risk) compared with 1 case in the 1,242 participants in the placebo group (less than 0.1%, less than 0.1 events per 100 patient years at risk). Nine of the 10 cases in the liraglutide group were graded as mild. Six participants (5 in the liraglutide group) had gallstone related pancreatitis.

The incidence of neoplasms was similar in the liraglutide group and placebo group (1.9 per 100 patient years at risk and 2.4 events per 100 patient years at risk, respectively). There were more cases of malignant and premalignant breast neoplasms in the liraglutide group (10 events in 9 women in the liraglutide group compared with 3 events in 3 women in the placebo group). Most women with events had above average weight loss. There were no cases of medullary thyroid carcinoma or C-cell hyperplasia and liraglutide treatment did not increase serum calcitonin concentrations. Four confirmed thyroid disease events occurred in 3 participants in the liraglutide group (3 cases of thyroid cancer and 1 case of autoimmune thyroiditis, which occurred after treatment had been stopped).

le Roux et al. 2017, was an extension study to Pi-Sunyer et al. 2015 which included participants diagnosed with prediabetes at baseline. Participants included in this extension study had liraglutide 3.0 mg for up to 160 weeks treatment. Again, gastro-intestinal disorders were the most common adverse events reported and the most common cause of withdrawal from the study (8% [118/1,501] in the liraglutide group compared with 2% [11/747] in the placebo group). Gallbladder related adverse events were more common with liraglutide than with placebo (5% [74/1,501] with liraglutide compared with 2% [13/747] with placebo). Pancreatitis and neoplasms were assessed over 172 weeks. There were 10 confirmed cases of pancreatitis in the liraglutide group (0.7%, 10/1,501) and 2 in the placebo group (0.3%, 2/747). Eight of the cases in the liraglutide group occurred during the first year of treatment. As seen in the 56-week period of the study (reported in Pi-Sunyer et al. 2015), more cases of malignant and pre-malignant breast neoplasms were reported in the liraglutide group than the placebo group (10 events in 9 women, 7 of which occurred in the first year of treatment, compared with no events in the placebo group).

Gastrointestinal adverse events were also the most common adverse events reported in Davies et al. 2015 and Blackman et al. 2016. In Davies et al. 2015, gastrointestinal disorders occurred more frequently in the liraglutide 3.0 mg group than the liraglutide 1.8 mg group (65.2% [275/422] compared with 56.2% [118/210]). There were more severe hypoglycaemic events in the liraglutide groups than the placebo group in Davies et al. 2015 (which was conducted in a population with type 2 diabetes). There were 5 events in 3 participants in the liraglutide 3.0 mg group, 3 events in 2 participants in the liraglutide 1.8 mg group and no events in the placebo group. All of the severe hypoglycaemic events occurred in participants who were taking concomitant sulfonylureas.

An overview of the results for safety and tolerability can be found in results tables.

Evidence strengths and limitations

The clinical development programme for liraglutide (Saxenda) for weight management included 4 double-blind RCTs, 3 of which are discussed in this evidence summary (Pi-Sunyer et al. 2015, Davies et al. 2015 and Blackman et al. 2016). A fourth RCT (le Roux et al. 2017), an extension of Pi-Sunyer et al. 2015, is also included. These RCTs included adults who were obese or overweight with a variety of weight-related co-morbidities including dyslipidaemia, hypertension, type 2 diabetes and sleep apnoea. In le Roux et al. 2017, participants had treatment with liraglutide 3.0 mg daily for up-to 160 weeks. In all of the studies, participants received regular structured lifestyle advice on weight loss interventions based on increasing physical activity and diet. It is unclear, if similar weight losses to those seen in the strictly controlled situations of clinical trials would be achievable in practice.

All of the studies discussed in this evidence summary compared liraglutide with placebo. There are no published double-blind RCTs which compare liraglutide (Saxenda) to other medicines for weight management. A phase II dose ranging RCT and extension study (Astrup et al. 2009 and Astrup et al. 2012) did include an orlistat arm. However, numbers in each treatment group were small and the orlistat arm of the study was open-label.

In Pi-Sunyer et al. 2015 and Davies et al. 2015 the primary outcomes on weight loss were assessed after 56 weeks treatment in all patients, which does not reflect the product license for liraglutide (Saxenda). The summary of product characteristics recommends that treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if patients have not lost at least 5% of their initial body weight. However, as highlighted in the EPAR for Saxenda, the 'stopping rule' for discontinuing liraglutide after 12 weeks in participants who have not responded to treatment to protect people from long-term use of a non-effective therapy, was only agreed during the marketing authorisation assessment process.

For all 4 studies, people who had taken part in an organised weight loss programme or taken any other medicine for weight management in the previous 3 months were excluded from the studies. In clinical practice, it is likely that adults who are being considered for treatment with liraglutide (Saxenda) for weight management will have previously tried other weight management options.

There was a high drop-out rate in all of the 4 studies discussed in this evidence summary. This ranged from 26% to 47% in the liraglutide 3.0 mg group and from 21% to 55% in the placebo group. In Pi-Sunyer et al. 2015, le Roux et al. 2017 and Blackman et al. 2016, missing values were accounted for using the last observation carried forward (LOCF) method, which carries forward the last post-baseline outcome or measurement for participants who have dropped out of the study. As

reported in the EPAR for Saxenda, LOCF is not considered to be a conservative method for dealing with missing data. For example, when considering the weight loss outcomes, it could be expected that after treatment discontinuation baseline weight would be reached again after a few weeks or months. The EPAR considered that baseline observation carried forward would be a more conservative method for dealing with missing data. Davies et al. 2015 used a multiple imputation method for missing data for the 3 co-primary outcomes, which may have reduced bias.

In le Roux et al. 2017, the primary outcome of time to type 2 diabetes was assessed at week 160. Participants and investigators were masked to treatment allocation during the entire trial (160 weeks plus the 12-week off treatment follow-up period). However, the manufacturers were unmasked to treatment allocation at week 56, which may have introduced bias. The manufacturers provided logistical support during the study, collected the data and performed the statistical analysis.

The primary outcome in Blackman et al. 2016, was change in the apnoea-hypopnea index (AHI: apnoea or hypopnea events per hour of sleep) from baseline. The outcome was assessed during an overnight clinic stay which may not be applicable to clinical practice. In addition, as highlighted in the EPAR interpretation of this outcome is difficult as there is no established minimal clinically importance difference for AHI.

In Davies et al. 2015, secondary endpoints were considered exploratory because no controls were applied for multiple comparisons. Comparisons between the liraglutide 1.8 mg and 3.0 mg doses were considered exploratory for the same reason. Pi-Sunyer et al. 2015, le Roux et al. 2017 and Blackman et al. 2016 also had no adjustments for multiple testing for the secondary outcomes. Therefore, any statistical analysis provided for these outcomes should be interpreted with caution.

The SPC for liraglutide (Saxenda) reports a number of patient groups for whom the safety and efficacy of liraglutide for weight management has not been established. This includes people aged 75 years and older, people with severe renal impairment, people with severe hepatic impairment, people with congestive heart failure class III to IV and people with obesity secondary to endocrine or eating disorders, or obesity caused by another medicinal treatment.

An overview of the quality assessment of each included study can be found in evidence tables.

Estimated impact for the NHS

Other pharmacological treatments

At the time of publication of this evidence summary, orlistat was the only other licensed pharmacological treatment for weight management available in the UK.

Costs of other pharmacological treatments

See table 3 for details.

Table 3 Costs of other treatment

Medicine/treatment	Usual dose	30-day cost excluding VAT
Liraglutide (Saxenda)	3.0 mg daily[a]	£196.20[b]
Orlistat	120 mg 3 times a day[a]	£18.05[c]
[a] Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the relevant SPC. [b] Costs based on MIMS, May 2017; excluding VAT [c] Costs based on Drug Tariff, May 2017; excluding VAT.		

Current or estimated usage

The manufacturer has reported that they will only promote the use of liraglutide (Saxenda) on private prescription, so they anticipate that use on the NHS will be limited. Consequently the manufacturer expects the impact for the NHS to be small (Novo Nordisk: source March 2017). The manufacturers have indicated that they do not intend to promote the use of liraglutide (Saxenda) within the NHS. This evidence summary does not contain recommendations from NICE on whether the medicine should be prescribed within the NHS or by private prescription.

Likely place in therapy

Liraglutide (Saxenda) is licensed as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of:

- 30 kg/m² or more (obese), or

- from 27 kg/m² to less than 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

The summary of product characteristics (SPC) recommends that treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if people have not lost at least 5% of their initial body weight.

Liraglutide (Saxenda) has been compared to placebo in randomised controlled trials (RCTs) but there are currently no published double-blind RCTs comparing it with other medicines for weight management. Studies have shown statistically significant weight losses with liraglutide compared with placebo in people with and without type 2 diabetes. However, as reported in the European Public Assessment Report (EPAR) for liraglutide (Saxenda) it is unlikely that any potential weight loss would be sustained after treatment with liraglutide is stopped. There were high dropout rates in both the liraglutide and placebo groups in all of the studies so continuation with treatment may be a problem in practice.

The NICE guideline on identifying, assessing and managing obesity recommends considering pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated. The guideline recommends to consider pharmacological treatment for people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes. At the time of publication of this evidence summary, orlistat was the only other licensed pharmacological treatment for weight management available in the UK. The guideline recommends orlistat only as part of a weight management plan in adults who are obese or have a BMI of 28 kg/m^2 or more with associated risk factors, such as type 2 diabetes. Liraglutide (Saxenda) is not specifically mentioned in the NICE guideline, however it is another potential pharmacological treatment option for use in-line with its marketing authorisation, for adults for whom lifestyle and behavioural approaches have not been effective and for whom the potential benefits of treatment outweigh the risks. The cost, mode of delivery and adverse effect profiles of the 2 treatments should be considered when choosing treatment options. Liraglutide is given by subcutaneous injection. Orlistat is an oral treatment, which may be preferable to some people. Orlistat and liraglutide have different adverse effect profiles; the SPC for orlistat (Xenical), lists gastrointestinal disorders including fatty or oily stools, faecal urgency and oily spotting from the rectum as very common adverse events; the liraglutide (Saxenda) SPC lists nausea, vomiting, diarrhoea and constipation as very common adverse events.

Liraglutide (Saxenda) is a different licensed product to liraglutide (Victoza), which has been licensed in the UK for the treatment of type 2 diabetes in adults since 2009. Victoza is not licensed as a pharmacological treatment for weight management and it also has a different licensed dose range.

In Davies et al. 2015, which was conducted in an overweight or obese population with type 2 diabetes, after 56 weeks' treatment, percentage body weight change from baseline was −6.0% in the liraglutide 3.0 mg group and −4.7% in the 1.8 mg group. However, this study was not designed to compare the 2 different doses of liraglutide. For people who are already using liraglutide (Victoza) for type 2 diabetes the EPAR for liraglutide (Saxenda) states that no data is available on switching from liraglutide 1.8 mg daily (Victoza) to liraglutide 3.0 mg daily (Saxenda) and therefore this cannot be recommended. Overall, the EPAR concluded that the higher liraglutide (Saxenda) dose did not appear to increase adverse event rates compared with the lower liraglutide (Victoza) dose, apart from gastrointestinal disorders, which were more frequent. The EPAR states however, that there is currently insufficient data to assess if uncommon events (pancreatitis/neoplasms) occur more frequently with liraglutide 3.0 mg daily compared with liraglutide 1.8 mg daily.

The SPC states that use of liraglutide for weight management in people with obesity secondary to endocrine or eating disorders, or obesity caused by another medicinal treatment is not recommended due to a lack of safety and efficacy data for use in these circumstances. The SPC also states that it is not recommended to use liraglutide (Saxenda) in conjunction with other pharmacological treatments for weight management.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

This use of liraglutide (Saxenda) is being considered for referral for a NICE technology appraisal. At the time of publication of this evidence summary a technology appraisal was not considered appropriate due to the intention of the manufacturers to only promote the use of liraglutide (Saxenda) on private prescription. The manufacturers have indicated that they do not intend to promote the use of liraglutide (Saxenda) within the NHS. This evidence summary does not contain recommendations from NICE on whether the medicine should be prescribed within the NHS or by private prescription.

NICE has issued guidelines on:

- Obesity: identification, assessment and management (2014) NICE guideline CG189
- Obesity prevention (2006) NICE guideline CG43
- Obesity: working with local communities (2012) NICE guideline PH42
- BMI: preventing ill health and premature death in black, Asian and other minority ethnic groups (2013) NICE guideline PH46
- Weight management: lifestyle services for overweight or obese adults (2014) NICE guideline PH53
- Preventing excess weight gain (2015) NICE guideline NG7
- Obesity prevention (2006) NICE guideline CG43
- Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy for treating morbid obesity (2016) NICE guideline IPG569
- Implantation of a duodenal–jejunal bypass sleeve for managing obesity (2013) NICE guideline IPG471
- Laparoscopic gastric plication for the treatment of severe obesity (2012) NICE guideline IPG432

A NICE technology appraisal on the use of naltrexone-bupropion prolonged release (European Public Assessment Report: Mysimba) for weight management in people who are obese or overweight with associated risk factors is in development with an expected publication date of August 2017.

NICE has also issued guidance on the use of liraglutide for type 2 diabetes:

- Type 2 diabetes in adults: management (2015) NICE guideline CG28.

References

Blackman A, Foster GD, Zammit G et al (2016) Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnoea: the SCALE Sleep Apnoea randomized clinical trial International Journal of Obesity 40 (8), 1310–19

Davies MJ, Bergenstal R, Bode B et al. (2015) Efficacy of liraglutide for weight loss among patients with type 2 diabetes. (The SCALE diabetes randomized clinical trial) Journal of American Medical Association 314 (7), 687–99

Pi-Sunyer X, Astrup A, Fujioka K et al. (2015) A Randomized, controlled trial of 3.0 mg of liraglutide in weight management New England Journal of Medicine 373 (1), 11–22

le Roux CW, Astrup A, Fujioka K et al. (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial The Lancet DOI.org/10.1016/so140-67361(17) 30069–7

Evidence tables

Table 4 Pi-Sunyer et al. 2015

Study references	Pi-Sunyer X, Astrup A, Fujioka K et al. (2015) A randomized, controlled trial of 3.0 mg of liraglutide in weight management –New England Journal of Medicine 373 (1), 11–22
Unique identifier	NCT01272219
Study type	RCT
Aim of the study	To evaluate the safety and efficacy of liraglutide as an adjunct to a reduced calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline
Study dates	June 2011 to March 2013
Setting	191 sites in 27 countries in Europe, North America, South America, Asia, Africa and Australia
Number of participants	n=3,731

Population	Adults aged 18 years and over with a stable body weight and either a BMI of 30 kg/m² or above or 27 kg/m² or above in addition to dyslipidaemia or hypertension. The mean age of participants was 45 years, the mean BMI was 38 kg/m², 78% of participants were female and 85% were white. All participants received lifestyle interventions for weight loss based on advice to increase physical activity to 150 minutes per week and reduce daily energy intake by 500 kcal below their individualised energy requirements.
Inclusion criteria	Adults with a BMI of 30 kg/m² or above or 27 kg/m² or above in addition to treated or untreated dyslipidaemia or hypertension. Participants had a stable body weight, defined as less than 5 kg self-reported change during the previous 3 months and had a previous failed dietary effort at weight loss.
Exclusion criteria	Exclusion criteria included adults with type 1 or type 2 diabetes, use of any medicines that can cause clinically significant weight changes, previous bariatric surgery, a history of pancreatitis, a history of major depression or another severe psychiatric disorder, a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma and previous treatment with a GLP-1 receptor agonist within the last 3 months. People who had taken part in an organised weight loss programme or taken any other medicines for weight management in the previous 3 months were also excluded from the study.
Intervention(s)	Liraglutide (n=2,487) injected subcutaneously, starting at a dose of 0.6 mg once daily increased to 3.0 mg once daily at 0.6 mg weekly increments[a]
Comparator(s)	Placebo (n=1,244) injected subcutaneously[a]
Length of follow-up	70 weeks[b]

Outcomes	Co-primary outcomes (all assessed at week 56): • weight change from baseline • proportion of participants who lost at least 5% of their baseline bodyweight • proportion of participants who lost more than 10% of their baseline bodyweight A fourth co-primary outcome on time to onset of type 2 diabetes over 160 weeks of treatment in the subgroup of people with prediabetes at baseline was assessed in le Roux et al. 2017	
	Secondary outcomes: • secondary outcomes include change from baseline in waist circumference, BMI, blood pressure, total lipid level concentrations and health-related quality of life scores	
	Safety outcomes: • Adverse events that occurred during the main 56 week trial period were reported that had an onset on or after the first day of treatment and no later than 14 days after the last day of treatment. Specific attention was given to types of adverse events that have an increased incidence in people with obesity or that are relevant to the GLP-1 agonist drug class.	
Source of funding	Novo Nordisk	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	Yes[a,c]
	Were participants, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes[d]
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes[e]

	How large was the treatment effect?	See table 8
	How precise was the estimate of the treatment effect?	See table 8
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See overview
Study limitations	• Study compares liraglutide to placebo and not active treatment. • The primary outcomes on weight loss are assessed after 56 weeks' treatment in all participants. Assessment of weight outcomes after 56 weeks is not reflective of the treatment indication in the summary of product characteristics (SPC: Saxenda), which recommends that treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if patients have not lost at least 5% of their initial body weight. • There was a high drop-out rate in the study; 28.1% in the liraglutide group and 35.6% in the placebo group. • No correction for multiple testing was made for the secondary outcomes. Therefore any statistical analysis provided for these outcomes should be interpreted with caution.	

Comments	[a] Randomisation to treatment was stratified according to prediabetes status at screening and according to BMI (less than 30 kg/m² and 30 kg/m² or more). Prediabetes was defined as either an HbA1c measurement from 39 to 46 mmol/mol or a fasting plasma glucose measurement from 5.6 to 6.9 mmol per litre or a 2 hour oral glucose tolerance test of 7.8 to 11.0 mmol per litre. [b] Participants were evaluated every 2 weeks until week 8, then every 4 weeks until week 44 and then again at weeks 50, 56, 60, 64, 68 and 70. The 3 co-primary outcomes and secondary outcomes were assessed at 56 weeks. [c] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (2:1) via a telephone or web based system provided by the manufacturers. [d] After 56 weeks, participants in the liraglutide group who did not have prediabetes at screening were randomly assigned in a 1:1 ratio to continue receiving liraglutide or to switch to placebo for 12 weeks to assess whether efficacy was maintained after discontinuation of liraglutide treatment and whether there were safety issues related to discontinuation. Participants in the placebo group continued to receive placebo. [e] There was a high dropout rate in the study. Missing values were imputed with the use of the last observation carried forward method for measurements made after baseline.
Abbreviations: GLP-1, glucagon-like peptide-1; HDL, high density lipoprotein; LDL, low density lipoprotein	

Table 5 le Roux et al. 2017

Study references	le Roux , Carel W, Astrup A et al. (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial The Lancet DOI.org/10.1016/S0140–67361(17) 30069–7
Unique identifier	NCT01272219
Study type	RCT
Aim of the study	To evaluate the effect of liraglutide 3.0 mg daily on the time to onset of type 2 diabetes and its effect on weight loss and safety over 3 years in a population of people with prediabetes

Study dates	June 2011 to March 2015
Setting	191 sites in 27 countries in Europe, North America, South America, Asia, Africa and Australia
Number of participants	n=2,254
Population	Adults aged 18 years and over with prediabetes, a stable body weight and either a BMI of 30 kg/m² or above or 27 kg/m² or above in addition to dyslipidaemia or hypertension. The mean age of participants was 47 years, the mean BMI was 39 kg/m^2 and the mean HbA1c was 40 mmol/mol in the liraglutide group and 39 mmol/mol in the placebo group. All participants received lifestyle interventions for weight loss based on advice to increase physical activity to 150 minutes per week and reduce daily energy intake by 500 kcal below their individualised energy requirements.
Inclusion criteria	Participants who had prediabetes[a] at baseline in Pi-Sunyer et al. 2015 and completed 56 weeks of treatment were enrolled onto this extension phase of the study.
Exclusion criteria	Exclusion criteria included adults with type 1 or type 2 diabetes, use of any medication that can cause clinically significant weight changes, previous bariatric surgery, a history of pancreatitis, a history of major depression or another severe psychiatric disorder, a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma and previous treatment with a GLP-1 receptor agonist within the last 3 months.
Intervention(s)	Liraglutide (n=1,505) injected subcutaneously, 3.0 mg once daily
Comparator(s)	Placebo (n=749) injected subcutaneously
Length of follow-up	172 weeks[b]
Outcomes	Primary outcome: time to onset of type 2 diabetes[a]
	Secondary outcomes: • secondary outcomes included change from baseline in bodyweight

	Safety outcomes: • adverse events that occurred during the main 160 week trial period were reported that had an onset on or after the first day of treatment and no later than 14 days after the last day of treatment	
Source of funding	Novo Nordisk	
Overall risk of bias/quality assessment (CASP RCT checklist**)**	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	Yes[c]
	Were participants, health workers and study personnel blinded?	Unclear[d]
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes[e]
	How large was the treatment effect?	See table 9
	How precise was the estimate of the treatment effect?	See table 9
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See overview

Study limitations	• Study compares liraglutide to placebo and not active treatment. • There was a high drop-out rate in the study; 47% in the liraglutide group and 55% in the placebo group. • The manufacturers were unmasked to treatment allocation at 56 weeks. • No corrections for multiple testing was made for the secondary outcomes. Therefore any statistical analysis provided for these outcomes should be interpreted with caution.
Comments	[a] Prediabetes was defined as either an HbA1c measurement from 39 to 46 mmol/mol or a fasting plasma glucose measurement from 5.6 to 6.9 mmol per litre or a 2-hour oral glucose tolerance test of 7.8 to 11.0 mmol per litre. A diagnosis of type 2 diabetes was made following 2 consecutive measurements of: an HbA1c of 48 mmol/mol and above, or a fasting plasma glucose concentration of 7.0 mmol per litre and above, or a 2 hour oral glucose tolerance test of 11.1 mmol per litre and above. [b] Participants had up to 160 weeks of treatment in total followed by a 12-week off-treatment follow up period. The primary and secondary outcomes were assessed at 160 weeks. [c] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (2:1) via a telephone or web based system provided by the manufacturers. [d] Participants and investigators were masked to treatment allocation during the entire trial (160 weeks plus the 12-week off treatment follow-up period). However, the manufacturers were unmasked to treatment allocation at week 56. [e] There was a high dropout rate from the study. Missing values were imputed with the use of the last observation carried forward method for measurements made after baseline.
Abbreviations: GLP-1, glucagon-like peptide-1	

Table 6 Davies et al. (2015)

Study reference	Davies M J, Bergenstal R, Bode B et al. (2015) Efficacy of liraglutide for weight loss among patients with type 2 diabetes. (The SCALE diabetes randomised clinical trial) Journal of American Medical Association 314 (7), 687–699
Unique identifier	NCT01272232
Study type	RCT
Aim of the study	To evaluate the safety and efficacy of liraglutide 3.0 mg daily as an adjunct to a reduced calorie diet and increased physical activity, for weight management in overweight or obese adults with type 2 diabetes
Study dates	June 2011 to January 2013
Setting	126 sites in 9 countries; France, Germany, Israel, South Africa, Spain, Sweden, Turkey and the UK (England and Scotland only)
Number of participants	n=846
Population	Adults aged 18 years and over with type 2 diabetes (mean duration of diabetes ranged from 6.7 to 7.5 years across the 3 groups in the study), a stable body weight and a BMI of 27 kg/m² or above. The mean age of participants was 55 years, the mean BMI was 37 kg/m², 50% of participants were female and 83% were white. All participants received lifestyle interventions for weight loss based on 150 minutes or more per week of brisk walking and a reduction in daily energy intake by 500 kcal below their individualised energy requirements.
Inclusion criteria	Adults with a BMI of 27 kg/m² and above and type 2 diabetes (HbA1c 53 to 86 mmol/mol), treated with diet and exercise alone or in combination with 1 to 3 oral hypoglycaemic agents. Around 11% of the group were being treated with diet and exercise only for type 2 diabetes and around 56% of the group were treated with metformin alone. Participants taking a sulfonylurea had their dose reduced by 50%. Participants had a stable body weight, defined as less than 5 kg change in weight during the previous 3 months.

Exclusion criteria	Exclusion criteria included treatment with GLP-1 agonists, insulin or any hypoglycaemic agents other than metformin, sulfonylurea or glitazones within the last 3 months, recurrent major hypoglycaemia, use of any medication that can cause clinically significant weight changes, previous surgical treatment for obesity, untreated or uncontrolled hypothyroidism or hyperthyroidism, known proliferative retinopathy or maculopathy requiring acute treatment, history of pancreatitis, a history of major depression or other severe psychiatric disorder, and a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. People who had taken part in an organised weight loss programme or taken any other medicines for weight management in the previous 3 months were also excluded from the study.
Intervention(s)	Liraglutide injected subcutaneously at a dose of either 3.0 mg (n=423) or 1.8 mg (n=211) once daily. Liraglutide was started at a dose of 0.6 mg once daily and increased at weekly increments of 0.6 mg until the treatment dose of 1.8 mg or 3.0 mg was reached[a,b]
Comparator(s)	Placebo (n=212) injected subcutaneously[a]
Length of follow-up	68 weeks[c]
Outcomes	Co-primary outcomes (all assessed at week 56 and based on fasting body weight): • relative change in body weight • proportion of participants who lost at least 5% of their baseline bodyweight • proportion of participants who lost more than 10% of their baseline bodyweight
	Secondary outcomes: • secondary outcomes included change from baseline in glycaemic control measures

	Safety outcomes: • safety and tolerability assessments included adverse events, standard laboratory tests, physical examinations, mental health questionnaires and ECGs	
Source of funding	Novo Nordisk	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	Yes[a,d]
	Were participants, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes[e]
	How large was the treatment effect?	See table 10
	How precise was the estimate of the treatment effect?	See table 10
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See overview

Study limitations	• Study compares liraglutide to placebo and not active treatment. • The primary outcomes on weight loss are assessed after 56 weeks' treatment. Assessment of weight outcomes after 56 weeks is not reflective of the treatment indication in the summary of product characteristics (SPC: Saxenda) which recommends that treatment should be discontinued after 12 weeks on the 3.0 mg daily dose (recommended maintenance dose) if patients have not lost at least 5% of their initial body weight. • There was a high drop-out rate in the study; 23.4% in the liraglutide 3.0 mg group, 22.3% in the liraglutide 1.8 mg group and 34.0% in the placebo group. • Secondary endpoints are to be considered exploratory because no controls were applied for multiple comparisons for the secondary outcomes.
Comments	[a] Randomisation to treatment was stratified according to the participants' baseline treatment for type 2 diabetes and baseline HbA1c level. [b] The results for the liraglutide 1.8 mg once daily group are not discussed in this evidence summary because this is not a licensed dose for this indication. [c] The 56-week study was followed by an observational 12-week off-drug follow up period to assess treatment cessation effects. [d] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (2:1:1) via an interactive voice or web based system. [e] There was a high dropout rate from the study. Missing values were imputed using a multiple imputation method for the 3 co-primary outcomes. Missing values for the secondary outcomes were imputed with the use of the last observation carried forward method for measurements made after baseline.
Abbreviations: ECG, electrocardiogram; GLP-1, glucagon-like peptide-1	

Table 7 Blackman et al. (2016)

Study reference	Blackman A, Foster GD, Zammit G et al (2016) Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnoea: the SCALE Sleep Apnoea randomized clinical trial International Journal of obesity 40 (8),1310–19

Unique identifier	NCT01557166
Study type	RCT
Aim of the study	To evaluate whether liraglutide 3.0 mg daily would reduce the severity of OSA compared with placebo in people with obesity and moderate or severe OSA who were unwilling or unable to use CPAP therapy.
Study dates	June 2012 to June 2013
Setting	40 sites in the US and Canada
Number of participants	n=359
Population	Adults with a stable body weight and a BMI of 30 kg/m² or above and moderate or severe OSA who were unwilling or unable to use CPAP therapy. The mean age of participants was 48 years, 72% of participants were male and 74% were white. All participants received lifestyle interventions for weight loss based on advice to increase physical activity to at least 150 minutes per week and reduce daily energy intake by 500 kcal below their individualised energy requirements.
Inclusion criteria	Adults aged 18 to 64 years with a BMI of 30 kg/m² and above, stable body weight (defined as less than 5% change in weight during the previous 3 months) and a diagnosis of moderate or severe OSA unwilling or unable to use CPAP or other positive airway pressure treatment. Moderate OSA was defined as an AHI of 15.0 to 29.9 apnoea or hypopnea events per hour of sleep; severe OSA was defined as an AHI of 30 or more events per hour of sleep.
Exclusion criteria	Exclusion criteria included adults with type 1 or type 2 diabetes, significant craniofacial abnormalities that may be causing OSA, relevant respiratory and neuromuscular disorders, use of any medication that can cause clinically significant weight changes, previous surgical treatment for obesity, history of pancreatitis and a history of major depression or other severe psychiatric disorder. People who had taken part in an organised weight loss programme or taken any other medicines for weight management in the previous 3 months were also excluded from the study.
Intervention(s)	Liraglutide (n=180) injected subcutaneously, starting at a dose of 0.6 mg once daily increased to 3.0 mg once daily at 0.6 mg weekly increments

Comparator(s)	Placebo (n=179) injected subcutaneously	
Length of follow-up	34 weeks[a]	
Outcomes	Primary outcome: change in AHI from baseline[b]	
	Secondary outcomes: • secondary outcomes included change from baseline in weight related outcomes	
	Safety outcomes: • safety and tolerability assessments included adverse events, standard laboratory tests, physical examinations, mental health questionnaires and ECGs	
Source of funding	Novo Nordisk	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	Yes[c]
	Were participants, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes[d]
	How large was the treatment effect?	See table 11
	How precise was the estimate of the treatment effect?	See table 11
	Can the results be applied in your context? (or to the local population)	Unclear[e]
	Were all clinically important outcomes considered?	Unclear[e]

	Are the benefits worth the harms and costs?	See overview
Study limitations	• Study compares liraglutide to placebo and not active treatment. • There was a high drop-out rate in the study; 26% in the liraglutide group and 21% in the placebo group. • There is no established minimal clinical important difference for AHI, making interpretation of this outcome difficult. • No adjustments were made for multiple testing for the secondary analyses. Therefore any statistical analysis provided for these outcomes should be interpreted with caution.	
Comments	[a] Treatment was for 32 weeks followed by a 2-week follow-up period. The primary outcome was assessed at week 32. [b] Change in AHI based on the American Academy of Sleep Medicine's 2007 definition with hypopnea requiring 30% or more reduction in nasal pressure signal excursions from baseline and 4% or more desaturation from pre-event baseline. AHI was assessed during overnight clinic stays at screening, week 12 and week 32. [c] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (1:1) via a telephone or web based system provided by the manufacturers. [d] There was a high dropout rate from the study. Missing values were imputed with the use of the last observation carried forward method for measurements made after baseline. [e] The relevance of the primary outcome to clinical practice is unclear. The outcome was assessed during an overnight clinic stay and there is no established minimal clinically importance difference.	
Abbreviations: AHI, apnoea-hypopnea index; CPAP, continuous positive airways pressure; OSA, obstructive sleep apnoea		

Results tables

Table 8 Pi-Sunyer et al. 2015

	Liraglutide 3.0 mg once daily	Placebo	Analysis
n[a]	2,437	1,225	
Co-primary outcomes			
Mean (SD) % change in body weight from baseline to week 56	−8.0% (6.7%)	−2.6% (5.7%)	Estimated treatment difference: −5.4% (95% CI −5.8% to −5.0%); p<0.001
Percentage of participants who lost 5% or more body weight from baseline to week 56	63.2%	27.1%	Estimated treatment difference: 36.1% OR: 4.8 (95% CI 4.1% to 5.6%); p<0.001
Percentage of participants who lost more than 10% body weight from baseline to week 56	33.1%	10.6%	Estimated treatment difference: 22.5% OR: 4.3 (95% CI 3.5% to 5.3%); p<0.001
Selected secondary outcomes			
Mean (SD) change in waist circumference from baseline (cm)	−8.2 (7.3)	−3.9 (6.6)	Estimated treatment difference: −4.2 (95% CI −4.7 to −3.7); p<0.001[b]
Mean (SD) change in BMI from baseline	−3.0 (2.6)	−1.0 (2.3)	Estimated treatment difference: −2.0 (95% CI −2.2 to −1.9); p<0.001[b]
Mean (SD) change in systolic blood pressure from baseline (mm Hg)	−4.2 (12.2)	−1.5 (12.4)	Estimated treatment difference: −2.8 (95% CI −3.56 to −2.09); p<0.001[b]
Mean percentage change in fasting total cholesterol from baseline[c]	−3.1%	−1.0%	Estimated treatment difference: −2.3% (95% CI −3.3% to −1.3%); p<0.001[b]
Mean (SD) change in IWQOL-Lite total score from baseline[d]	10.6 (13.3)	7.7 (12.8)	Estimated treatment difference: 3.1 (95% CI 2.2 to 4.0); p<0.001[b]
Safety and tolerability outcomes			
n[e]	2,481	1,242	

Participants with an adverse event that occurred in at least 5% of participants	80.3% (1992/ 2,481)	63.3% (786/ 1,242)	No statistical analysis reported for safety outcomes
Participants with a severe adverse event that occurred in at least 0.2% of participants	6.2% (154/ 2,481)	5.0% (62/ 1,242)	
Participants who withdrew from study due to adverse events	9.9% (246/ 2,487)	3.8% (47/ 1,244)	
Nausea	40.2% (997/ 2,481)	14.7% (183/ 1,242)	
[a] Efficacy analyses were based on the full-analysis set, which included all participants who underwent randomisation and received at least 1 dose of the study drug and had at least 1 assessment after baseline. [b] No adjustments were made for multiple testing for the secondary analyses. Therefore any statistical analysis provided for these outcomes should be interpreted with caution. [c] Standard deviation for this outcome not provided in paper. [d] IWQOL-Lite is a validated, 31-item, self-reported measure of obesity-specific quality of life measured in 5 domains (physical function, self-esteem, sexual life, public distress and work). Higher scores indicate better quality of life. [e] The safety analysis set included all participants who were randomised to a study drug and received at least 1 dose.			
Abbreviations: CI, confidence interval; IWQOL-Lite, impact of weight on quality of life-lite version; OR, odds ratio; SD, standard deviation			

Table 9 le Roux et al. 2017

	Liraglutide 3.0 mg once daily	Placebo	Analysis
n[a]	1,472	738	
Primary outcome			

Time to onset of type 2 diabetesover 160-week study period[b]	Number of participants diagnosed with type 2 diabetes: 2% (26/ 1,472)	Number of participants diagnosed with type 2 diabetes: 6% (46/738)	HR: 0.21 (95% CI 0.13 to 0.34); p<0.0001
Selected secondary outcomes			
Mean (SD) % change in body weight from baseline to week 160	−6.1% (7.3%)	− 1.9% (6.3%)	Estimated treatment difference −4.3% (95% CI −4.9% to −3.7%); p<0.0001[c]
Safety and tolerability outcomes			
n[d]	**1501**	**747**	
Participants with adverse events	95% (1,421/1,501)	89% (668/747)	No statistical analysis reported for safety outcomes
Participants with serious adverse events	15% (227/1,501)	13% (96/747)	
Participants who withdrew from study due to adverse events	13% (199/1,501)	6% (46/747)	

[a] Efficacy analyses were based on the full-analysis set, which included all participants who underwent randomisation, received at least 1 treatment dose and had at least 1 post-baseline assessment.

[b] Prediabetes was defined as either an HbA1c measurement from 39 to 46 mmol/mol or a fasting plasma glucose measurement from 5.6 to 6.9 mmol per litre or a 2 hour oral glucose tolerance test of 7.8 to 11.0 mmol per litre. At baseline, the mean HbA1c was 40 mmol/mol in the liraglutide group and 39 mmol/mol in the placebo group. A diagnosis of type 2 diabetes was made following 2 consecutive measurements of: a HbA1c of 48 mmol/mol and above, or a fasting plasma glucose concentration of 7.0 mmol per litre and above or a 2 hour oral glucose tolerance test of 11.1 mmol per litre and above.

[c] No adjustments were made for multiple testing for the secondary analyses. Therefore any statistical analysis provided for these outcomes should be interpreted with caution.

[d] The safety analysis set included all participants who were randomised to a study drug and received at least 1 dose.

Abbreviations: CI, confidence interval; SD, standard deviation

Table 10 Davies et al. 2015

	Liraglutide 3.0 mg once daily	Placebo	Analysis
n[a]	412	211	
Co-primary outcomes			
Estimated mean % change in body weight from baseline to week 56	−6.0%	−2.0%	Estimated treatment difference: −4.0% (95% CI −5.1% to −2.9%); p<0.001
Percentage of participants who lost 5% or more body weight from baseline to week 56	54.3%	21.4%	Estimated treatment difference: 32.9% (95% CI 24.6% to 41.2%); p<0.001
Percentage of participants who lost more than 10% body weight from baseline to week 56	25.2%	6.7%	Estimated treatment difference: 18.5% (95% CI 12.7% to 24.4%); p<0.001
Selected secondary outcomes			

Percentage of participants with a HbA1c less than 53 mmol/mol after 56 weeks' treatment	69.2% (278/411)	27.2% (56/211)	Estimated treatment difference: 42% OR: 8.79 (95% CI 5.74 to 13.44); p<0.001[b]
Safety and tolerability outcomes			
n[c]	422	212	
Participants with treatment-emergent adverse events	92.9% (392/422)	85.8% (182/212)	No statistical analysis reported for safety outcomes
Participants with serious treatment emergent adverse events	8.8% (37/422)	6.1% (13/212)	
Participants who withdrew from study due to adverse events	9.2% (39/422)	3.3% (7/212)	
Participants with gastrointestinal disorder adverse events	65.2% (275/422)	39.2% (83/212)	
[a] Efficacy analyses were based on the full-analysis set, which included all participants who underwent randomisation and received at least 1 dose of the study drug and had at least 1 assessment after baseline [b] The study authors described these secondary outcomes as exploratory. No adjustments were made for multiple testing for the secondary analyses. Therefore any statistical analysis provided for these outcomes should be interpreted with caution. [c] The safety analysis set included all participants who were randomised to a study drug and received at least 1 dose			
Abbreviations: CI, confidence interval; OR, odds ratio			

Table 11 Blackman et al. 2016

	Liraglutide 3.0 mg once daily	Placebo	Analysis
n[a]	180	179	

Primary outcome			
Mean (SE) change from baseline to week 32 in AHI (events per hour of sleep)[b]	−12.2 (1.8)	−6.1 (2.0)	Estimated treatment difference: −6.1 (95% CI −11.0 to −1.2); p=0.015
Selected secondary outcomes			
Mean (SE) % change in body weight from baseline to week 32	−5.7% (0.4%)	− 1.6% (0.3%)	Estimated treatment difference −4.2% (95% CI −5.2% to −3.1%); p<0.0001[c]
Safety and tolerability outcomes			
n[d]	176	179	
Participants with adverse events[e]	80.1%	69.3%	No statistical analysis reported for safety outcomes
Participants with serious adverse events	3.4% (6/176)	3.4% (6/179)	
Participants who withdrew from study due to adverse events	11.4% (20/176)	3.4% (6/179)	

[a] Efficacy analyses were based on the full-analysis set, which included all participants who underwent randomisation.

[b] Change in AHI based on the American Academy of Sleep Medicine's 2007 definition with hypopnea requiring 30% or more reduction in nasal pressure signal excursions from baseline and 4% or more desaturation from pre-event baseline. At baseline, mean (SE) AHI was 49.0 (27.5) apnoea or hypopnea events per hour of sleep in the liraglutide group and 49.3 (27.5) in the placebo group.

[c] No adjustments were made for multiple testing for the secondary analyses. Therefore any statistical analysis provided for these outcomes should be interpreted with caution.

[d] The safety analysis set included all participants who were randomised to a study drug and received at least 1 dose.

[e] Number of participants for this outcome in each group not provided in study paper.

Abbreviations: AHI, apnoea-hypopnea index (apnoea or hypopnea events per hour of sleep); CI, confidence interval; SE, standard error

Excluded studies

Study reference	Reason for exclusion
Astrup A, Carraro R, Finer N et al. (2012) Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog liraglutide International Journal of Obesity 36 (6), 843–54	Study not prioritised (not the best available evidence: phase II dose finding study)
Astrup A, Rössner S, Van Gaal L et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study Lancet 374 (9701), 1606–16	Study not prioritised (not the best available evidence: phase II dose finding study)
Wadden TA, Hollander P, Klein S et al. (2013) Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study International Journal of Obesity 37 (11), 1443–51	Study not prioritised (not the best available evidence: based on participant selection and number of participants in study)
Kolotkin RL, Fujioka K, Wolden M L et al. (2016) Improvements in health-related quality of life with liraglutide 3.0 mg compared with placebo in weight management Clinical Obesity 6 (4), 233–42	Study not prioritised (not best available evidence: additional analysis from Pi-Sunyer et al. 2015 study)
Lean ME. J, Carraro R, Finer N et al. (2014) Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. International Journal of Obesity38 (5), 689–97	Study not prioritised (not the best available evidence: results from phase II dose finding study)

Terms used in this evidence summary

Apnoea-hypopnea index (AHI)

Number of apnoea or hypopnea events per hour of sleep. Change in AHI was based on the American Academy of Sleep Medicine's 2007 definition with hypopnea requiring 30% or more reduction in nasal pressure signal excursions from baseline and 4% or more desaturation from pre-event baseline.

Search strategy

Database: Medline, including Medline in-process; epubs ahead of print and daily update

Platform: Ovid

Version: 1950 – 15th February 2017

Search date:16th February 2017

Number of results retrieved: 266

Search strategy:

1 exp Obesity/ (171895)

2 Overweight/ (18158)

3 (obes* or "excess weight" or overweight or "over weight" or bmi or "body mass index" or fat or "waist circumference" or adiposity).tw. (520429)

4 1 or 2 or 3 (552307)

5 Liraglutide/ (985)

6 liraglutide.tw. (1517)

7 Saxenda.tw. (14)

8 NN2211.tw. (25)

9 "NN 2211".tw. (3)

10 5 or 6 or 7 or 8 or 9 (1670)

11 Randomized Controlled Trial.pt. (450371)

12 Controlled Clinical Trial.pt. (92108)

13 Clinical Trial.pt. (511384)

14 exp Clinical Trials as Topic/ (305434)

15 Placebos/ (34250)

16 Random Allocation/ (90113)

17 Double-Blind Method/ (143695)

18 Single-Blind Method/ (23797)

19 Cross-Over Studies/ (40938)

20 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1003833)

21 (random$ adj3 allocat$).tw. (28607)

22 placebo$.tw. (190095)

23 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (153211)

24 (crossover$ or (cross adj over$)).tw. (74287)

25 or/11-24 (1723984)

26 animals/ not humans/ (4293002)

27 25 not 26 (1616243)

28 4 and 10 and 27 (266)

Database: Embase

Platform: Ovid

Version: 1974 to February 15th 2017

Search date: 16th February 2017

Number of results retrieved: 677

Search strategy:

1 exp Obesity/ (429276)

2 (obes* or "excess weight" or overweight or "over weight" or bmi or "body mass index" or fat or "waist circumference" or adiposity).tw. (747574)

3 1 or 2 (844832)

4 Liraglutide/ (5419)

5 liraglutide.tw. (3048)

6 Saxenda.tw. (71)

7 NN2211.tw. (35)

8 "NN 2211".tw. (148)

9 4 or 5 or 6 or 7 or 8 (5477)

10 exp Clinical Trials/ (277587)

11 Randomization/ (84845)

12 Placebo/ (332970)

13 Double Blind Procedure/ (141141)

14 Single Blind Procedure/ (29689)

15 Crossover Procedure/ (55263)

16 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1329073)

17 (random$ adj3 allocat$).tw. (34601)

18 placebo$.tw. (253854)

19 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (199809)

20 (crossover$ or (cross adj over$)).tw. (87361)

21 or/10-20 (1788869)

22 nonhuman/ not human/ (3757460)

23 21 not 22 (1729033)

24 3 and 9 and 23 (1071)

25 limit 24 to english (1049)

26 limit 25 to (conference abstract or conference paper or conference proceeding or "conference review" or editorial or note or short survey) (372)

27 25 not 26 (677)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – 2 of 2, February 2017

DARE – 2 of 4, April 2015 (legacy database)

CENTRAL – 1 of 12, January 2017

HTA – 4 of 4, October 2016

NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 16th February 2017

Number of results retrieved: CDSR – 1; DARE – 0; CENTRAL – 259; HTA – 2; NHS EED – 0.

Search strategy:

ID Search

#1 [mh obesity]

#2 [mh ^overweight]

#3 (obes* or "excess weight" or overweight or "over weight" or bmi or "body mass index" or fat or "waist circumference" or adiposity):ti,ab

#4 #1 or #2 or #3

#5 [mh ^liraglutide]

#6 liraglutide:ti,ab

#7 saxenda:ti,ab

#8 NN2211:ti,ab

#9 "NN 2211":ti,ab

#10 #5 or #6 or #7 or #8 or #9

#11 #4 and #10

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Carly Anna Hughes: Board member Active Norfolk physical activity provider, GP advisor to Kastech (unpaid), lecture income from International medical press, hospitality from Nutricia, Cambridge Weight Plan and LighterLife, consultancy provided to Orexigen, Mundipharma and Ethicon, one education meeting supported by Novo Nordisk (no personal payment), representative for Association for study of obesity Eastern Region, GP with interest in obesity group member, World obesity national SCOPE fellow and founder Norfolk Obesity Network

Lucy Turnbull: Chair of British Dietetic Association obesity group

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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