New Medicine Recommendation
Liraglutide (Saxenda▼)

For use as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (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.

Recommendation: BLACK

NOT recommended for use by the NHS in Lancashire.
There is insufficient evidence of long-term safety, sustained weight loss and cost effectiveness in patients using Saxenda®▼.

Includes medicines that NICE has not recommended for use and terminated technology appraisals, unless there is a local need.
This category includes medicines for which there is insufficient evidence of their effectiveness.

Summary of supporting evidence

- Five randomized, placebo-controlled trials of liraglutide for weight management were identified, four of which were double blinded. All trials were carried out over at least 32 weeks.
- In addition to recommended diet and physical activity, liraglutide consistently resulted in a 4 to 6 kg weight loss, with a greater proportion of patients achieving at least 5 and 10% weight loss compared with placebo. Clinically important weight loss is traditionally defined as loss of more than 5 percent of usual body weight over six months. In the past, an absolute weight loss of 10 pounds (4.5 kg) or more was also accepted as a criterion for significant weight loss. However, this definition is inadequate given the increase in average body size in most developed countries. These relatively arbitrary historical standards need more rigorous assessment since traditional definitions do not distinguish between losses to lean body mass (sarcopenia) or body fat, which can lead to important clinical outcomes. It is therefore important to bear this in mind when considering the clinical significance of the weight loss achieved.
- Although weight loss was maintained in the studies among completers, further studies are required to establish whether these effects are maintained with continuing treatment in the longer term. Participants in the trials regained weight after cessation of treatment, indicating that continued treatment is necessary to sustain the on-drug benefits, although the treatment difference was still significant at week 172.9,11
- In the trials all subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, which may not be truly representative of a real life clinical setting
- The most common adverse effects were gastrointestinal and primarily occurred early in the treatment course.
- Additional studies are needed to determine its long term efficacy and safety
Details of Review

Name of medicine (generic & brand name):
Liraglutide (Saxenda▼)

Strengths and forms:
6mg/ml solution for injection, 3ml pre-filled pen

Dose and administration:
The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least one week intervals to improve gastro-intestinal tolerability (see table 1). If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended.

Table 1 Dose escalation schedule

<table>
<thead>
<tr>
<th>Dose escalation 4 weeks</th>
<th>Dose</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.6mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.2mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.8mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.4mg</td>
<td>1</td>
</tr>
</tbody>
</table>

Maintenance Dose 3.0mg

Saxenda should not be used in combination with another GLP-1 receptor agonist.

When initiating Saxenda, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia.

BNF therapeutic class / mode of action: Chapter 1.8 Gastro-intestinal system, Obesity

Liraglutide (Saxenda▼) is a once-daily glucagon-like peptide-1 (GLP-1) analogue with 97% similarity to naturally occurring human GLP-1, a hormone that is released in response to food intake. Like human GLP-1, liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption, thereby leading to reduced food intake. Liraglutide (Saxenda) is currently not listed in the BNF for treatment of obesity (April 2017)

Licensed indication(s):
Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (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.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

Proposed use:
Within licensed indication
Course and cost:
Price 18 mg /3ml solution for injection in prefilled pen, 5=£196.20

Current standard of care/comparator therapies:
A sustainable weight management programme which includes strategies to change behaviour, increase physical activity, and improve diet and eating behaviour.\(^5\)

An anti-obesity drug should be considered only for those with a BMI of ≥ 30 kg/m\(^2\), in whom diet, exercise and behaviour changes fail to achieve a realistic reduction in weight. In the presence of associated risk factors, it may be appropriate to prescribe an anti-obesity drug to individuals with a BMI of ≥ 28 kg/m\(^2\), (this weight falls into overweight classification as defined by NICE 25-29.9kg/m\(^2\)).\(^3\)

Orlistat, is the only licensed drug currently available in the UK that is recommended specifically for the management of obesity; it acts by reducing the absorption of dietary fat.

Orlistat is licensed for use as an adjunct in the management of obesity in patients with a BMI of ≥ 30 kg/m\(^2\), or, in individuals with a BMI of ≥ 28 kg/m\(^2\) in the presence of other risk factors.

Relevant NICE guidance:
Not yet reviewed by NICE.

NICE CG189 (Obesity: identification, assessment and management) Nov 2014.\(^3\)This guideline covers identifying, assessing and managing obesity in children (aged 2 years and over), young people and adults. It aims to improve the use of bariatric surgery and very-low-calorie diets to help people who are obese to reduce their weight.

A NICE Medicines Evidence Commentary published December 2015.\(^4\)

A NICE evidence summary (ESNM) has an anticipated publication date of June 2017.

Disease Background
Obesity is one of the most significant public health challenges globally. Its impact is considerable in the Western world and it is now also an emerging epidemic in developing countries. Overweight and obesity are commonly classified using the body mass index (BMI), calculated as weight in kilograms divided by the square of height in metres. More than one-third of adults in the US and in countries across Europe are classified as obese, defined as a BMI of 30 kg/m\(^2\)or greater, and 30-70% are overweight, with a BMI of 25-29.9 kg/m\(^2\).\(^5\)

Obesity has many serious health consequences, and a decreased life expectancy of 5—10 years, which make reducing its high prevalence a public health priority. It is a chronic condition associated with major comorbidities that include hypertension, hyperglycaemia, dyslipidaemia, certain types of cancer, obstructive sleep apnoea (OSA) and atherosclerosis. Obesity and overweight are also independent risk factors for myocardial infarction and ischaemic heart disease, the leading cause of death worldwide. The relationship between obesity and type 2 diabetes mellitus (T2DM) is well established, and the global obesity epidemic largely explains the 3-fold increase in the rates of T2DM in recent years. Obesity-related pre-diabetes increases the risk of developing T2DM 5-to 6-fold. It is also estimated that up to 5% of adults in Western countries may have undiagnosed OSA, and up to 20% may have at least mild OSA. Obesity adversely affects physical and mental health and reduces quality of life. Obese individuals often suffer from physical symptoms, such as joint pain, and psychosocial problems.

In 2015, the mid-year population estimate for the Lancashire area was 1,478,115.\(^6\) Using
data on overweight and obesity among adults (defined as people aged 16 and over) from the Health Survey for England (HSE) 2015, which found 62.9% of adults to be overweight or obese (67.8% of men and 58.1% of women), and currently 26.9% of adults (aged 16 or over) are classified as obese. The obesity prevalence appears to be increasing and by 2050 obesity is predicted to affect 60% of adult men, 50% of adult women and 25% of children.

This would indicate that within Lancashire there is currently an overweight / obese population of approximately 929,734 (this population will include a percentage of overweight patients whose BMI is 25-27 kg/m$^2$ for whom liraglutide (Saxenda) is not licensed for use) and an obese population of 397,613.

**Current treatment options**

The decision to start drug treatments should be made after discussing the potential benefits and limitations with the person, including the mode of action, adverse effects and monitoring requirements, and the potential impact on the person’s motivation. Arrangements should be made for appropriate healthcare professionals to offer information, support and counselling on additional diet, physical activity and behavioural strategies when drug treatment is prescribed. Information should be provided on patient support programmes.

Orlistat is a gastrointestinal lipase inhibitor that has been on the market since 1998. Whilst it has shown moderate beneficial effects on weight loss and blood pressure, orlistat is associated with an array of side effects that limit its tolerability, including steatorrhoea, faecal incontinence and rectal discharge. Historically, several new products for the treatment of obesity have been authorised in the EU and US, but also been withdrawn or their marketing authorisation has been suspended due to safety issues. The co-prescribing of orlistat with other drugs aimed at weight reduction is not recommended.

Liraglutide is in a different pharmacological class to the other weight management products currently or previously approved, with a different mechanism of action.

**Summary of efficacy data in proposed use:**

**Pivotal studies**

The clinical development programme to evaluate the efficacy of liraglutide for weight management includes one phase 2 dose-finding trial (trial 1807) and four confirmatory phase 3 trials (trials 1839, 1922, 3970 and 1923), conducted worldwide and involving 5813 obese (BMI of ≥30 kg/m$^2$) or overweight (BMI of ≥27 kg/m$^2$) subjects with or without T2DM. All were randomised, double-blind, placebo-controlled trials. The clinical trial programme was designed both to assess the weight loss potential of liraglutide in several different clinical situations and to assess its effects on some of the comorbidities associated with obesity. Each of the trials had a specific focus that in composite allows a full understanding of the efficacy and safety of liraglutide in the treatment of obesity.

Three of the phase 3 trials (trials 1839, 1922 and 1923) were of 56 weeks duration (52 weeks exposure on target dose). The primary endpoints of the trials were related to body weight, and included both mean and categorical changes in body weight. In trial 1807, orlistat was included as an open label comparator, the others were placebo-controlled studies. Since weight control can be achieved by a reducing diet, exercise and behaviour modification alone, the use of a placebo group is necessary to show clearly that the drug and appropriate non pharmacological treatments are more effective than the same non pharmacological treatment alone.

**Trial 1807 (The phase 2 trial)** was designed to establish the most efficacious dose of liraglutide after an initial 20 weeks period of exposure followed by an interim analysis at...
52 weeks, which was included to assess the persistence of response over 52 weeks. The full 104-week trial period provided an initial evaluation of long-term safety beyond one year.\(^5\)

The 3.0 mg dose was selected prior to the phase 3 trials and implemented throughout. The long-term data in trial 1807 are, however, based on treatment with 2.4 mg during part of the treatment period based on a preliminary choice. The sample size calculation was reasonable for a Phase 2 trial. The trial lacks sensitivity to dose-responsiveness of rare adverse events.\(^5\)

**Results Summary**

The dose selection for Phase 3 trials is based on the results of trial 1807 (supported by trial 1922), confirm that weight loss is dose dependent and that the highest dose tested (3.0mg) is the most efficacious. The primary endpoint (at weeks 20 and 52) was the change in body weight (kg) from baseline with a secondary endpoint of proportion of subjects achieving >5% reduction of baseline body weight. **At 20 weeks** patients on 3mg liraglutide had a mean weight loss of 7.15kg from baseline compared to losses of 2.76kg with placebo and 4.12kg with Orlistat (p=0.0000). The percentage of patients achieving >5% reduction of baseline body weight was 76.1% with 3mg liraglutide, versus 29.6% with placebo and 44.2% with Orlistat (p=0.0000). **At 52 weeks** patients on 3mg liraglutide had a mean weight loss of 8.9kg from baseline compared to losses of 2.7kg (p=0.0000) with placebo and 4.7kg with orlistat (p= 0.0001). The percentage of patients achieving >5% reduction of baseline body weight was 75% with 3mg liraglutide, versus 27.6% with placebo (p=0.0000) and 45.3% with orlistat (p=0.0001)\(^5\)

**Trial 1839, (SCALE Obesity and pre-diabetes)**, the largest in the programme, was focused specifically on weight loss (56 weeks) and the effects of liraglutide on preventing progression of pre-diabetes to T2DM (an additional 104-week treatment period for subjects at high risk of developing diabetes [i.e. subjects with pre-diabetes at screening]).\(^9\) The 56 week part of this trial assessed body weight loss in all the 3,731 randomised patients (2,590 completers).

The 160 week part of this trial assessed time to onset of type 2 diabetes in the 2,254 randomised patients with pre-diabetes (1,128 completers).All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, including 12-week re-randomised period.

**Results Summary**

The primary endpoint at 56 weeks was the change in bodyweight from baseline (% and kg) with secondary endpoints of the proportion of subjects achieving ≥5% / ≥10% reduction of baseline body weight. At 56 weeks, patients in the 3mg Liraglutide group had lost a mean of 8.4±7.3kg (7.98%) of body weight and those in the placebo group had lost a mean of 2.8±6.5kg (2.62%) (p=< 0.001). A total of 63.2% of the patients in the Liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (p<0.001), and 33.1% and 10.6% respectively, lost more than 10% of their body weight(p<0.001).\(^9\)

Early responders were defined as patients who achieved ≥5% weight loss after 12 weeks on treatment dose of liraglutide. In the 56 week part of the study, 67.5% achieved ≥5% weight loss after 12 weeks. For patients who have achieved a weight loss of <5% after 12 weeks on treatment dose of liraglutide, the proportion of patients not reaching a weight loss of ≥10% after 1 year was 93.4%.\(^5\)

In the 160 weeks part of the study, weight loss occurred mainly in the first year, and was sustained throughout 160 weeks. A post hoc analysis showed that the risk of diabetes was about 66% lower with liraglutide compared with placebo after the 160 weeks.\(^{16}\)

**Trial 1922, (SCALE Diabetes),** specifically focused on the effect of two different doses of liraglutide (3mg and 1.8mg – the currently licensed dose for treatment of T2DM) vs
placebo, on weight loss and glycaemic control in subjects (846 randomised (628 completers)) with obesity and diagnosed T2DM. All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, including the 12-week follow-up period.

The study was not powered to enable definitive conclusions about safety to be made.

Results Summary

The primary endpoint at 56 weeks was the change in bodyweight from baseline (% and kg) with secondary endpoints of the proportion of subjects achieving ≥5% / ≥10% reduction of baseline body weight. At 56 weeks, patients in the 3mg liraglutide group had lost a mean of 6.24 kg (5.9%) of body weight and those in the placebo group had lost a mean of 2.13 kg (2.0%) (p=< 0.0001). A total of 49.9% of the patients in the 3mg liraglutide group as compared with 35.6% and 13.8% in the 1.8mg liraglutide and placebo groups respectively, lost at least 5% of their body weight (p<0.0001), and 23.4%, 14.4% and 4.3% respectively, lost more than 10% of their body weight (p<0.0001).5

Trial 1923, (SCALE Maintenance), was designed specifically to assess the ability of 3mg liraglutide to maintain weight loss induced by a low-calorie diet (LCD) in 422 randomised (305 completers) obese and overweight patients with hypertension or dyslipidaemia after a preceding weight loss of ≥5% induced by a low calorie diet11. All subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial from randomisation, including the follow-up period. The design of trial SCALE Maintenance allowed separating the effects of non-pharmacological means and liraglutide.

Results Summary

The primary endpoint at 56 weeks was the change in body weight from randomisation (after LCD run-in period) (%) with secondary endpoints of the proportion of subjects that maintained the ≥ 5% reduction in initial body weight achieved during the LCD run-in period and the proportion of subjects achieving ≥ 5% reduction of baseline body weight. At 56 weeks, patients in the liraglutide group had lost a mean of 6.11% of body weight and those in the placebo group had lost a mean of 0.05% (p=< 0.0001). More patients receiving liraglutide maintained the ≥ 5% reduction in body weight achieved during the LCD run-in period than those receiving placebo 46.4% and 20.9%,5 respectively (p=<0.0001) (using modified intent to treat with LOCF) and the proportion of patients achieving ≥ 5% reduction of randomisation body weight was 26.1% in the liraglutide group and 6.3% in the placebo group (p=<0.0001)5

Trial 3970, (SCALE Sleep Apnoea), conducted in in 359 randomised (276 completers) subjects with obstructive sleep apnoea (OSA), was a 32-weeks trial as the maximal weight loss with liraglutide was expected around 32 weeks based on the findings of trials 1807 and 192312.

Results Summary

The primary end point was the change from baseline in apnea-hypopnea index (AHI) events per hour, with secondary endpoints of change (%) in fasting body weight from baseline to week 32, proportion of 5% responders from baseline to week 32 and proportion of 10% responders from baseline to week 32. After 32 weeks, the mean reduction in AHI was greater with 3mg Liraglutide than with placebo, -12.2 vs -6.1 events per hour (p= 0.0150). Liraglutide produced greater mean percentage weight loss from baseline compared to placebo, -5.7% vs -1.6% (p<0.0001) and the proportion of 5% responders was 46.4% for liraglutide compared to 18.1% for the placebo group (p<0.0001), whilst the proportion of 10% responders was 22.4% for liraglutide and 1.5% for placebo (p<0.0001).5

The interpretation of the sleep-apnoea related parameters is difficult, as there is no established margin for clinical relevance. The decrease in AHI was closely correlated to
weight loss, as was known from literature. The decrease in sleep apnoea episodes was accompanied by statistically non-significant changes in the patient-reported outcomes.\(^5\)

Overall conclusions on the clinical efficacy

When interpreting the results from the SCALE trials it should be borne in mind that although the majority of baseline characteristics are consistent with the expected target clinical population, some sub-populations would appear to be under represented:

- Subjects with BMI $<$ 30 kg/m\(^2\) were only 5.4% of the study population
- Subjects $\geq$ 65 years of age were only 6.6% of the population and only 0.4% of the participants were $\geq$ 75 years. The oldest patient was 82 years.
- Races other than White or Black (African American) represented 4.9% of participants

In the mITT pooled analysis using LOCF, after treatment with liraglutide 3.0 mg, mean weight loss was 7.5% (7.8 kg) with liraglutide 3.0 mg vs. 2.3% (2.5 kg) with placebo, a placebo-subtracted weight loss of 5.2%. The mean treatment difference in trials 3970 SCALE sleep apnoea (4.15%) and 1922 SCALE Diabetes (3.95%) was less than in the pooled dataset (5.24%). A possible explanation is that trial 3970 SCALE sleep apnoea had a shorter treatment duration of 32 weeks (compared to 56 weeks for the other trials) and the subjects may not have reached the full treatment effect and trial 1922 SCALE Diabetes was conducted in T2DM patients who are known to respond less to weight reduction attempts. When applying more conservative methods than LOCF imputation for missing data, a treatment effect of -4.28% is estimated. The results regarding weight loss were consistent in most subgroups. However, the treatment estimate for females (-5.83%) was better compared to males (-3.56%) (a statistically significant interaction, p<0.0001). The difference can be attributed to lower exposure in males (only 28.8% of the overall trial populations). As discussed above, the treatment effect in T2DM as assessed in trial 1922 (-3.95%) was less than in all 1-year trials (-5.24%), and there was a high proportion of males in this trial. After correction for gender effects, the interaction is no longer statistically significant (p=0.1762) and is not considered to pose any clinical problems.

Overall the SCALE trials demonstrate that superior weight loss was achieved with liraglutide compared to placebo in obese/overweight patients in all groups studied. Across the trial populations, greater proportions of the patients achieved $\geq$ 5% and $>$ 10% weight loss with liraglutide than with placebo.

Summary of safety data:

In the completed studies, liraglutide was administered to a total of 5813 obese patients or overweight patients with at least one weight related co-morbidity. The most frequently observed side effects for liraglutide were gastrointestinal in nature (nausea, vomiting, diarrhoea and constipation).

The SPC for liraglutide (Saxenda) lists the following adverse events:\(^1\)

<table>
<thead>
<tr>
<th>Incidence of Event</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common (≥2/10)</td>
<td>Nausea, vomiting, diarrhoea, constipation</td>
</tr>
<tr>
<td>Common (≥2/100 to &lt;1/10)</td>
<td>Hypoglycaemia*, insomnia**, dizziness, dysgeusia, dry mouth, dyspepsia, gastritis, gastro-oesophageal reflux disease, upper abdominal pain, flatulence, eructation, abdominal distension, cholelithiasis***, injection site reactions, asthenia, fatigue, increased lipase, increased amylase</td>
</tr>
<tr>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>Dehydration, tachycardia, pancreatitis***, cholecystitis***, urticaria, malaise</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Rare (≥ 1/10,000 to ≤ 1/1,000)</td>
<td>Anaphylactic reaction, acute renal failure, renal impairment</td>
</tr>
</tbody>
</table>

* Hypoglycaemia - In clinical trials in overweight or obese patients without type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, no severe hypoglycaemic events (requiring third party assistance) were reported. Symptoms of hypoglycaemic events were reported by 1.6% of patients treated with Saxenda and 1.1% of patients treated with placebo; however, these events were not confirmed by blood glucose measurements. The majority of events were mild.

In a clinical trial in overweight or obese patients with type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, severe hypoglycaemia (requiring third party assistance) was reported by 0.7% of patients treated with Saxenda and only in patients concomitantly treated with sulfonylurea. Also, in these patients documented symptomatic hypoglycaemia was reported by 43.6% of patients treated with Saxenda and in 27.3% of patients treated with placebo. Among patients not concomitantly treated with sulfonylurea, 15.7% of patients treated with Saxenda and 7.6% of patients treated with placebo reported documented symptomatic hypoglycaemic events (defined as plasma glucose ≤3.9 mmol/L accompanied by symptoms).

**Insomnia was mainly seen during the first 3 months of treatment

*** Use of GLP-1 receptor agonists has been associated with the risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with liraglutide. Caution should be exercised in patients with a history of pancreatitis.

In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. The fact that substantial weight loss can increase the risk of cholelithiasis and thereby cholecystitis only partially explained the higher rate with liraglutide. Cholelithiasis and cholecystitis may lead to hospitalisation and cholecystectomy.

The EMEA concluded in its public assessment report that the general AE profile is in line with the experience with Victoza (liraglutide 1.8mg for treatment of T2DM).

Current data are insufficient to assess if uncommon events (pancreatitis, neoplasms) occur more frequently with Saxenda’s higher dose (3.0 mg) compared to the dose in T2DM (1.8 mg).

The consistent finding that GLP-1 analogues increase the pulse rate has caused concern with respect to cardiovascular safety. It seems that the increase in pulse rate is not dose dependant. There are data that GLP-1 receptors are present in the cardiac pacemaker suggesting a direct effect of liraglutide on the heart. The maximum increase in pulse rate is 4.5 bpm for liraglutide (compared to placebo 1.1 bpm) after 6 weeks and slightly declined thereafter. The effect persists until end-of-trial and is then 2.8 bpm above placebo. There is no indication of a dose response.

The period of maximum effect on pulse rate is well covered by the safety database; however less information is available with respect to (very) long term effects of the increase in pulse. Because the effect on pulse is not strongly related to dose and seems to be a class effect, information from the large cardiovascular safety trials with liraglutide (LEADER) and other GLP-1 analogues is relevant. However, the LEADER trial only investigates the 1.8mg dose in a population of patients who were at high risk for cardiovascular events and who had a baseline glycated haemoglobin level of 7% or more, the observed benefits and risks may therefore not apply to patients at lower risk.

Gall bladder events occur more frequently with 3.0 mg compared to 1.8 mg.
Strengths and limitations of the evidence:

**Strengths:**
- All the pivotal trials were randomised, double-blind and placebo-controlled
- Large study populations
- At least 32 week duration for clinical studies

**Limitations:**
- Use of last observation carried forward imputation in the pre-specified primary analyses
- Some of the studies were not powered correctly to enable conclusions to be drawn regarding clinical efficacy / safety.
- Although weight loss was maintained in the studies among completers, further studies are required to establish whether these effects are maintained with continuing treatment in the longer term. Participants in the trials regained weight after cessation of treatment, indicating that continued treatment is necessary to sustain the on-drug benefits.
- In the trials all subjects were on a 500 kcal/day energy-deficit diet and increased physical activity programme throughout the trial, which may not be truly representative of a real life clinical setting.
- In the pooled dataset, the rate of withdrawals is high, 29.6% with a low follow up at 56 weeks, (missing endpoint data for 21.7% of subjects)

Prescribing and risk management issues:

The higher weight management liraglutide dose in comparison to the diabetes dose seems to have little effect on the AE rate, except for gastrointestinal events which are more frequent. The comparisons in the dose-finding trial 1807 and trial 1922 were not powered to assess the rates of rare events such as pancreatitis, cardiovascular events and neoplasms.

There is no evidence of an overall increased number of malignancies in the weight management program; the numbers of events were too low for sound statistical analysis and some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (e.g. breast).

The Summary of product characteristics cites various special warnings and precautions for use for liraglutide (Saxenda) covering its use in patients with a history of / or the following active conditions:
- Congestive heart failure, severe renal impairment, hepatic impairment, inflammatory bowel disease, diabetic gastroparesis, pancreatitis, cholelithiasis and cholecystitis, thyroid disease.

Heart rate should be monitored at regular intervals and patients advised of potential risk of dehydration and to take precautions to avoid fluid depletion.

Patients with type 2 diabetes mellitus receiving liraglutide in combination with a sulfonylurea may have an increased risk of hypoglycaemia.

The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least one week intervals to improve gastro-intestinal tolerability (see table 1, page 5). If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended.
Liraglutide (Saxenda) is a ‘black triangle’ medicine - the Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected adverse reactions (side effects) to newer drugs and vaccines, which are denoted by the Black Triangle symbol.\textsuperscript{14}

**Commissioning considerations:**

Orlistat, is the only licensed drug currently available in the UK that is recommended specifically for the management of obesity and the prescribing data in the table below is drawn from the available ePACT Data.

**Prescribing of Orlistat across Lancashire March 2016 to February 2017**

<table>
<thead>
<tr>
<th>BNF Name</th>
<th>Items</th>
<th>Cost</th>
<th>Cost/item</th>
<th>Total Quantity x Items</th>
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</thead>
<tbody>
<tr>
<td>Alli (60mg)</td>
<td>1</td>
<td>£11.96</td>
<td>£11.96</td>
<td>28</td>
</tr>
<tr>
<td>Beacita (120mg)</td>
<td>1</td>
<td>£29.29</td>
<td>£29.29</td>
<td>84</td>
</tr>
<tr>
<td>Orlistat (60mg)</td>
<td>71</td>
<td>£2,169.28</td>
<td>£30.55</td>
<td>6,742</td>
</tr>
<tr>
<td>Orlistat (120mg)</td>
<td>15,903</td>
<td>£297,063.44</td>
<td>£18.68</td>
<td>1,378,955</td>
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<tr>
<td>Xenical (120mg)</td>
<td>114</td>
<td>£3,421.93</td>
<td>£30.02</td>
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<tr>
<td><strong>Totals</strong></td>
<td>16,090</td>
<td>£302,695.91</td>
<td>£18.81</td>
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</tr>
</tbody>
</table>

On examination of these figures it would appear that each item of Orlistat equates approximately to 28 days treatment (exception Alli).

From the ePACT data the average cost / item for the period March 2016 – February 2017 is £18.81. The category M price in the NHS Drug Tariff (January 2017) for Orlistat is £17.55 for 84 capsules (28 days’ supply)

The cost of Orlistat per patient per year is £228.15 (based on the drug tariff price)

Using the above Epact data and assuming that patients take Orlistat on a regular basis for a full year, there are approximately 1,327 patients taking orlistat in Lancashire.

If the potential obese patient population in Lancashire is taken as 397,613 then the currently treated patient population represents only 0.33% of the potential patient pool. In reality this percentage might be smaller as Orlistat will have been prescribed for a percentage of patients who are classified as overweight and not obese i.e. BMI $\geq 28$kg/m$^2$ $\leq 30$kg/m$^2$

Liraglutide (Saxenda) 18 mg/3ml soln for inj in prefilled pen, 5=£196.20.

Once on maintenance dose of 3mg / day, one pre filled pen will last 6 days, a box of 5 pre filled pens will therefore allow treatment for 30 days i.e. 1 month.

Annual cost = 12 x £196.20 = £2,354.40 per patient.

This represents over a ten fold increase in cost from that currently of orlistat.

There is also the possibility that more overweight / obese patients will be treated with Saxenda than are currently treated with orlistat, due to the once daily administration (vs up to 3 times daily with Orlistat), patient acceptability of side effects, the fact that liraglutide (Saxenda) is licensed for use in patients over 27kg/m$^2$ in the presence of at least one weight related comorbidity (orlistat for patients over 28kg/m$^2$) and due to the fact that the overweight / obese population is increasing.

**Anticipated patient numbers and net budget impact**

Data on overweight and obesity among adults (defined as people aged 16 and over) from the Health Survey for England (HSE) 2015, states 62.9% of adults to be overweight or obese (67.8% of men and 58.1% of women)\textsuperscript{7}

In 2015, the population of Lancashire was estimated at 1,478,115\textsuperscript{6}indicating a potential
overweight / obese patient population of 929,734 and an obese population of 397,613.

If 100% patients (1,327) currently treated with Orlistat have their treatment changed to Liraglutide then the annual cost of treatment will rise from £302,695 to £3,124,289.

If 50% patients (671) currently treated with Orlistat have their treatment changed to Liraglutide and 50% remain on Orlistat, then the annual cost of treatment will rise from £302,695 to £1,713,492.

The annual cost of liraglutide (Saxenda) per 100,000 population with a 62.9% obesity would be £148,091,760

To treat 10% of the obese population with liraglutide (Saxenda) would cost £14,809,176

There is also the real possibility of an increase in the numbers of patients being treated with Liraglutide (Saxenda) for obesity / overweight in the future due to the better patient acceptability (more acceptable AE profile, once daily administration) and an increasing overweight / obese population.

**Associated additional costs or available discounts:**

None identified

**Productivity, service delivery, implementation:**

It is anticipated that patients being considered for treatment with Saxenda would be on tier 3 or 4 of the obesity care pathway.¹⁵

**Innovation, need, equity:**

Liraglutide (Saxenda) will offer an additional pharmacological treatment option for the management of patients classified as obese or overweight with associated co-morbidities.
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<tr>
<th>Levels</th>
<th>Criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Patient-oriented evidence from:</td>
<td>High quality individual RCT = allocation concealed, blinding if</td>
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<tr>
<td></td>
<td>high quality randomised controlled trials (RCTs) with low risk of bias</td>
<td>possible, intention-to-treat analysis, adequate statistical</td>
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<td>systematic reviews or meta-analyses of RCTs with consistent findings</td>
<td>power, adequate follow-up (greater than 80%)</td>
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<tr>
<td>Level 2</td>
<td>Patient-oriented evidence from:</td>
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<td>clinical trials at moderate or high risk of bias</td>
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<td>systematic reviews or meta-analyses of such clinical trials or with</td>
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<td>cohort studies</td>
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<td>case-control studies</td>
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<td>Level 3</td>
<td>Disease-oriented evidence, or evidence from:</td>
<td>Any trial with disease-oriented evidence is Level 3,</td>
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<td>consensus guidelines</td>
<td>irrespective of quality</td>
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<td>expert opinion</td>
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<tr>
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<td>case series</td>
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