NHS Bedfordshire Clinical Commissioning Group

NHS Luton Clinical Commissioning Group

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

February 2016

Review: February 2019

Bulletin 231 : Liraglutide (Saxenda®) for obesity

JPC Recommendations:

To support the East of England Priorities Advisory Committee (PAC) policy statement and recommendations (See attachment)

The East of England
Priorities Advisory Committee
A function of PrescQIPP

FULL EVIDENCE REVIEW

Liraglutide (Saxenda®) for obesity

Interim PAC recommendations pending the UK launch of liraglutide (Saxenda ®) for the treatment of obesity

- Treatment of obesity with liraglutide (including off label use of liraglutide (Victoza®)) is currently NOT recommended for routine commissioning because of:
  - Insufficient evidence in relation to long term efficacy and long term safety.
  - Safety concerns regarding serious adverse effects including pancreatitis.
  - Unavailability of information on cost effectiveness and cost impact.
  - Recommendations and place in therapy will be reviewed in the light of new national guidance, new evidence and information on cost effectiveness.

Medicine	Liraglutide (Saxendav®) for obesity.
Proposed sector of prescribing	Primary and secondary care

Key points/Evidence level

Key points

- Being overweight and obese represent a rapidly growing threat to the health of populations globally. Obesity is a risk factor for coronary heart disease, hypertension and stroke, type 2 diabetes mellitus (T2DM), certain cancers, dyslipidaemia, osteoarthritis, gout, and pulmonary diseases, including sleep apnoea.
- Obesity is also a psychosocial and social burden, often resulting in social stigma, depression, low self-esteem, reduced mobility and a generally poorer quality of life. Obesity reduces life expectancy by an average of three years.
- In England, in 2011, 65% of adult males and 58% of adult females were thought to be overweight or obese (24% of males and 26% of females were classified as obese).
- Obesity can result in a considerable cost to the NHS not least because of its associated risk factors and potential to contribute to cardiovascular, metabolic and other diseases.
- The approach to preventing and managing obesity is multifaceted. Treatments include weight management programmes (i.e. dietary advice and weight loss targets, physical activity programmes, behavioural interventions and psychological support), pharmacological therapy and surgery.

- Pharmacological therapy should only be considered for patients who have already attempted to lose weight through weight management programmes.
- Available therapeutic treatments for obesity are currently limited to orlistat.
- The combination product naltrexone/bupropion in addition to a reduced calorie diet and physical activity has been approved by both the EMA and FDA for treatment of obesity and will become a further therapeutic option when available.
- Liraglutide (Victoza®) is already licensed for use in T2DM up to a maximum dose of 1.8 mg/day. NICE advises that doses above 1.2 mg/day are not recommended in T2DM. In obesity, liraglutide is used at a higher dose (3mg per day) than in diabetes.
- Five clinical studies provide the main evidence for efficacy and safety of liraglutide at a dose of 3mg in overweight/obese subjects with or without comorbidities and with or without T2DM. Only two of the reported studies are currently fully published.
- A Phase II dose ranging randomised controlled trial investigated four strengths of liraglutide compared with placebo (double blind) and open label orlistat (120mg t.d.s.) for 20 weeks (n = 564). Having demonstrated short term weight loss, safety, tolerability and long term efficacy were evaluated in an 82 week extension increasing to the higher dose of liraglutide 3mg daily compared with open label orlistat. At 52 weeks, liraglutide 3mg recipients lost 5.8kg more weight than those on placebo and 3.8kg (1.6-6.0) more than those on orlistat. At 104 weeks, participants on liraglutide lost 3.0kg (1.3-4.7) more weight than those on orlistat.
- The Phase III SCALE Programme consists of three 56 week studies assessing the effects of liraglutide 3mg daily vs. placebo on weight loss in overweight/obese patients with or without comorbidities and with or without T2DM and one 32 week study in sleep apnoea.
- Overall, results from the five studies suggest that liraglutide led to a 7.5% reduction in body weight compared with a 2.3% reduction in subjects taking placebo.
- Liraglutide was generally well tolerated. The most commonly reported events from all these studies were mainly GI related. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo.
- The efficacy of liraglutide 3mg daily has been demonstrated against placebo and orlistat for one year in the Phase III studies with a small number of patients receiving the 3mg dose for up to two years in the Phase II study.
- There is a lack of data to suggest improvement in cardiovascular outcomes and the sustainability of weight loss and glucose control in the long term. There are also concerns regarding increased risk of pancreatitis, effects on the gall bladder, thyroid tumours and potential effects on heart rate.
- There is limited comparative evidence versus alternative treatments – only the Phase II study compares liraglutide with an alternative therapeutic intervention (orlistat).
- There is also lack of data to demonstrate beneficial impact on wider outcomes including hospital admissions and potential impact on public health.
- There is no relevant national guidance in relation to use of liraglutide (Saxenda®) for obesity at the time of writing.
- It is difficult to assess the impact per 100,000 population at this time.
- Pricing details for liraglutide (Saxenda®) are not currently available.
- Feedback from East of England clinicians has indicated that there may be a place for the use of liraglutide (Saxenda®) in a small group of patients in tier 4 specialist obesity centres. Further work needs to be done on launch of the product to establish its place in therapy.

Introduction

- Obesity is a serious and challenging threat to public health across global populations. Obesity is directly linked to a number of different illnesses including T2DM, fatty liver disease, hypertension, gallstones and gastro-oesophageal reflux disease as well as psychological and psychiatric morbidities.[1]
- Obesity and overweight (pre-obese) are conditions in which weight gain has reached the point where it poses significant risks to health. Obesity is more than a lifestyle disorder.
- Obesity may be considered as a disease and a risk factor for other diseases (e.g. T2DM). In adults, the body mass index (BMI) is frequently used as a measure of overweight and obesity, with overweight being defined as a BMI 25-29.9 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2.
- In England in 2011, 65% of adult males and 58% of adult females were thought to be overweight or obese (24% of males and 26% of females were classified as obese).[2]
- Treatments for obesity include weight management programmes (i.e. dietary advice and weight loss targets, physical activity programmes, behavioural interventions and psychological support), pharmacological therapy and surgery.[1-3]
- The only pharmacological therapy currently licensed for the treatment of obesity is orlistat; treatment should be considered as an adjunct to lifestyle interventions for people with a BMI ≥30kg/m^2, or a BMI ≥28kg/m^2 and associated risk factors (e.g. T2DM, hypertension, dyslipidaemia). Surgery is a first-line option in adults with a BMI ≥50kg/m^2.[2]
- Evidence suggests that glucagon-like peptide-1 (GLP-1) receptor agonists which are already licensed for management of T2DM (through their clinical effect on HbA1c) are also effective in promoting weight loss in overweight and obese subjects, with or without diabetes and with or without comorbidities.[4-8]
- In people with BMI 25-35 kg/m^2, a 5-10% weight loss is required to produce a clinically significant reduction in cardiovascular disease and metabolic risk.[2]

The intervention mechanism of action

Liraglutide is an analogue of the natural hormone glucagon-like peptide-1 (GLP-1). GLP-1 is a gut hormone released into the circulation after meal ingestion, which stimulates insulin and inhibits glucagon release. GLP-1 can suppress food intake and appetite and decelerate gastric emptying and induce satiety thus reducing appetite and food intake.[2,7]

Liraglutide is a GLP-1 analogue with an attached acyl chain which allows non-covalent binding to albumin. This delays both the inactivation of liraglutide by dipeptidyl peptidase 4 and renal clearance, extending the half-life of GLP-1 from one to two minutes for native GLP-1 to 11–15 hours allowing once daily administration. In T2DM, liraglutide has been shown to improve glycaemic control, reducing glycosylated haemoglobin A1c (HbA1c), and reducing body weight.[2]

Licensed indication

Liraglutide, is already licensed as Victoza® for the treatment of T2DM at a maximum dose of 1.8mg.[9] However, NICE advises that doses above 1.2mg are not used in this indication as there was no evidence of added benefit at the higher dose.[10]

NB: Liraglutide (Victoza®) is only recommended in by NICE in T2DM for use in triple therapy in patients with HbA1c ≥7.5% and BMI >35kg/m^2 or, if BMI < 35kg/m^2 only where insulin therapy would have significant occupational implications or would benefit other significant obesity-related co-morbidities. It is recommended in dual therapy regimens only if a person is intolerant to an alternative hypoglycaemic agent.[10]

In obesity, liraglutide is used at a higher dose (3mg per day) than in diabetes.

The EU approval for this new indication comes within a month of the US Food and Drug Administration also approving it for use in obesity.[11,12]

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

- ≥ 30 kg/m² (obese), or
- ≥ 27 kg/m² to < 30 kg/m² (overweight)

in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or T2DM), hypertension, dyslipidaemia or obstructive sleep apnoea.[13]

Treatment with Saxenda should be discontinued after 12 weeks on the 3mg/day dose if patients have not lost at least five percent of their initial body weight.[13]

Formulation/Available products

Saxenda® 6 mg/ml solution for injection in pre-filled pen for subcutaneous use.

One mL of solution contains 6mg of liraglutide*.

One pre-filled pen contains 18mg liraglutide in 3ml.

* human GLP-1 analogue produced by recombinant DNA technology in saccharomyces cerevisiae.[13]

Usual dosage

The usual dose is 3mg daily.

The starting dose is 0.6 mg daily. The dose should be increased to 3mg daily in increments of 0.6mg with at least one week intervals to improve gastro-intestinal tolerability. If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment.[13]

Daily doses higher than 3mg are not recommended.

Saxenda® is for subcutaneous use only.[13]

Treatment alternatives/place in therapy

Treatments for obesity include weight management programmes (i.e. dietary advice and weight loss targets, physical activity programmes, behavioural interventions and psychological support), pharmacological therapy and surgery.[1-3]

Pharmacological therapy should only be considered for patients who have seriously attempted to lose weight through weight management programmes.[1,3,14]

The only pharmacological therapy currently licensed in the UK for the treatment of obesity is orlistat. Drug treatment with orlistat should be considered as an adjunct to lifestyle interventions for people with a BMI ≥30kg/m^2, or a BMI ≥28kg/m^2 and associated risk factors (such as type 2 diabetes, hypertension, or dyslipidaemia).[1,3,14]

Weight-loss surgery may be an option if non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least six months in people with a BMI ≥40 kg/m^2, or a BMI ≥35kg/m^2 and other significant co-morbidities that could be improved if they lost weight.[3,15]

Future alternatives

Both the FDA and the EMA have recently approved the prolonged release combination product naltrexone/bupropion (US - Contrave, EU – Mysimba) in addition to a reduced calorie diet and physical activity.

Several safety and tolerability concerns identified with Mysimba were related to central nervous system and gastrointestinal adverse events, and uncertainties with regard to cardiovascular outcomes in the longer term.[16]

This is the second obesity formulation to be approved in Europe, within the same timeframe as the marketing authorization for liraglutide (Saxenda®). This will provide physicians treating obesity in Europe with two new therapeutic options which remain to be utilised in clinical practice in addition to orlistat.

NB: Phentermine with topiramate for treatment in obesity was refused a CHMP authorisation in 2012 and the licensing application for lorcaserin was withdrawn in May 2013. NICE technology appraisals in development for both drugs were subsequently suspended.[17,18]

National guidance

No relevant national guidance was identified for the use of liraglutide in obesity.

Approach to weight loss management for obesity is generally multifactorial.

- Several NICE guidelines on the prevention and management of overweight individuals and obesity have been developed and implemented by NICE.[1,15,19,20]
- Managers and health professionals in all primary care settings should ensure that preventing and managing obesity is a priority at both strategic and delivery levels.[1]
- NICE also makes recommendations on behaviours and activities that may help people maintain a healthy weight or prevent excess weight gain in adults and children.[19]
- NICE provides recommendations for commissioners and providers of lifestyle weight management programmes and health and social care professionals who advise or refer people to these programmes.[20]
- The NICE guideline 'Obesity: identification, assessment and management of overweight and obesity in children, young people and adults' offers best practice advice on the care of adults and children who are overweight or obese.[15]

Treatments for obesity include weight management programmes (i.e. dietary advice and weight loss targets, physical activity programmes, behavioural interventions and psychological support), pharmacological therapy and surgery.

Pharmacological therapy (with orlistat) is normally only considered for patients who have attempted to lose weight and as an adjunct to lifestyle interventions for people with a BMI ≥30kg/m^2, or a BMI ≥28kg/m^2 and associated risk factors.[1]

Drugs should never be used as the sole element of treatment.

Treatment with orlistat should only be continued beyond 12 months after discussing potential benefits and risks with the patient.[14]

Local guidance

None identified.

Evidence for use

Trials summary

The effectiveness of liraglutide (Saxenda®) was shown in five clinical trials involving over 5,800 obese or overweight patients. All patients also received counselling on diet and physical activity. [11] Only two of the reported studies are currently fully published.

A published Phase II dose ranging study investigated four strengths of liraglutide compared with placebo and orlistat on bodyweight and tolerability in obese individuals (BMI 30-40 kg/m^2) without

T2DM for 20 weeks. Liraglutide 1.2mg, vs 1.8mg, vs. 2.4mg vs. 3mg vs. placebo (double blind) were compared with open label orlistat (120mg t.d.s.) (n =564). The primary endpoint was weight change analysed by intention to treat.[21,22] All groups included a reduced-calorie diet and increased physical activity. This is the only study where direct comparison with an alternative therapeutic intervention (orlistat) is made.

At 20 weeks, participants on liraglutide lost significantly more weight than did those on placebo ($p<0.003$ for liraglutide 1.2mg and $p<0.0001$ for liraglutide 1.8-3mg) and orlistat ($p<0.003$ for liraglutide 2.4mg and $p<0.0001$ for liraglutide 3mg). Mean weight loss with liraglutide 1.2-3mg was 4.8kg, 5.5kg, 6.3kg, and 7.2kg compared with 2.8kg with placebo and 4.1kg with orlistat.[2,22]

More individuals (76%) lost ≥5% weight with liraglutide 3mg that with placebo (30%) or orlistat (44%). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84-96%) with 1.8-3mg/day.

Safety, tolerability and long-term efficacy were evaluated over two years in an 82 week study extension.[23] The sponsor was unblinded at 20 weeks and participants/investigators at one year. After one year, liraglutide/placebo recipients were switched to liraglutide 2.4mg, then 3mg (based on 20-week and one-year results, respectively).

Of 564 adults enrolled in the 20 week study, 398 entered the extension and 268 completed the two-year trial. The primary outcome was mean change in body weight at week 104.

At 52 weeks, liraglutide 3mg recipients lost 5.8kg more weight than those on placebo and 3.8kg (1.6-6.0) more than those on orlistat ($p>0.0001$; ITT LOCF). At 104 weeks, participants on liraglutide 2.4/3mg for the full two2 years lost 3.0kg (1.3-4.7) more weight than those on orlistat ($p<0.001$).[23]

With liraglutide 2.4/3 mg, the 2-year prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, with improvements in blood pressure and lipids.[23]

Novo Nordisk's Phase 3 development programme, SCALE™ (Satiety and Clinical Adiposity – Liraglutide Evidence in Non-diabetic and Diabetic people) consisted of three, 56 week placebo-controlled trials plus a 32 week SCALE™ Sleep Apnoea study.

The trials included overweight people (BMI ≥27 kg/m^2) with comorbidities, e.g. hypertension, dyslipidaemia, or T2DM, or obese people (BMI ≥30 kg/m^2), with or without comorbidities. All studies all involved a reduced-calorie diet and increased physical activity. Only the SCALE Maintenance has to date been fully published.

SCALE obesity and pre-diabetes study

Inclusion criteria: Overweight / obese individuals (BMI ≥27 with ≥1 comorbidity or ≥30) without T2DM randomised 2:1 to liraglutide 3mg (n=2487) or placebo (n=1244) as an adjunct to diet and exercise. Primary outcomes were change in body weight > 5%, change in body weight > 10% and proportion with onset of T2DM at 160 weeks.

The overall weight loss at 56 weeks was 8% in the liraglutide group compared with 2.6% on placebo ($p<0.0001$), the difference being 5.4%.[24] Reduction in body weight ≥ 5% was 64% in liraglutide group vs. 27% in the placebo group ($p<0.0001$). Reduction in body weight ≥ 10% was 33% vs. 10.6% ($p>0.0001$) in the liraglutide and placebo groups respectively.[2,24,25]

Weight loss responders also had greater improvements across a range of efficacy outcomes (e.g. waist circumference fasting plasma glucose and systolic blood pressure) although this is to be expected as a benefit of weight reduction. Results for proportion of patients with pre-diabetes at baseline developing T2DM remain to be reported.[24]

SCALE diabetes study

Investigated liraglutide (1.8mg or 3mg daily) in obese or overweight subjects with T2DM. Treatment was added onto background diabetes treatment. Participant inclusion criteria were overweight/

obese individuals (BMI ≥27) with T2DM randomised 2:1:1 to liraglutide 3mg, liraglutide 1.8mg or placebo as an adjunct to diet and exercise (n = 847).

Primary outcomes were change from baseline body weight and proportion of subjects losing ≥ 5%, and ≥ 10% in body weight. Overall weight loss at 56 weeks was 5.9% in the liraglutide 3.0mg group compared with 4.6% in the liraglutide 1.8mg (p< 0.01) and 2.0% in the placebo group (p < 0.0001).[26]

Reported reductions in body weight ≥ 5% were 50%, 35% and 13% in liraglutide 3mg, 1.8mg and placebo groups respectively (p<0.001 and p<0.0001) and reported reductions ≥ 10% were 22%, 13% and 4% in liraglutide 3mg, 1.8mg and placebo groups respectively (p<0.01 and p <0.0001 respectively).[2,26,27]

During the 12 week follow up people in both liraglutide groups experienced moderate weight gain.

The SCALE Maintenance Study assessed the efficacy of liraglutide 3mg vs. placebo in maintaining weight loss achieved with a low-calorie diet (n = 422). Participant inclusion criteria were overweight/ obese individuals (BMI ≥30 or BMI ≥27 with co-morbidities following dietary weight loss of ≥ 5% and stable bodyweight during previous three months). Diet and exercise counselling were provided throughout the trial.

Co-primary outcomes were change from baseline body weight and proportion of subjects losing ≥ 5%, in body weight at week 56.

The overall weight loss was 6.1% in the liraglutide 3mg group compared with 0.1 % in the placebo group (p<0.0001).[28,29] The proportion of patients who lost ≥5% in body weight was 50.5% in the liraglutide group compared with 21.9% in the placebo group (p>0.0001). Proportions of patients who maintained their run in weight loss were 81.4% and 48.9% respectively (p<0.0001).

Liraglutide also produced small but statistically significant improvements in several cardiometabolic risk factors compared with placebo.

The SCALE Sleep Apnoea Study compared the effects of liraglutide 3mg versus placebo on obstructive sleep apnoea as an adjunct to diet and exercise (n = 359).

Primary outcome was change in apnoea-hypoapnoea Index (AHI) after 32 weeks. Inclusion criteria were obese individuals without diabetes with moderate (AHI 15-29.9 events/h) or severe AHI ≥ 30 events/h) obstructive sleep apnoea. Reduction in AHI was 12.2 vs. 6.1 events for liraglutide 3mg compared with placebo. Mean percentage weight loss was 5.7% vs 1.6% respectively.[30,31]

The most commonly reported events from all of these studies were mainly GI related. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo. Adverse events were reported to be mainly transient and rarely led to discontinuation of treatment.

Statistical analysis of the SCALE studies used ITT analysis and the Last Observation Carried Forward (LOCF) method (i.e. all randomised and exposed subjects who have been exposed to one dose of trial product). The FDA advises against use of LCOF in analysis because of potential to distort and bias study data.

Looking at the results of the five studies together, liraglutide at a daily dose of 3mg led to a 7.5% reduction in body weight, compared with a 2.3% reduction in patients taking placebo. Patients treated with liraglutide had a continuous decrease in body weight during the first 40 weeks of treatment, after which the weight loss achieved was maintained.[32,33]

When the figures for the main studies were re-analysed using a more conservative method that assumed that patients who did not complete the studies (around 30%) would not have seen any improvement, similar but smaller weight reductions with liraglutide were noted.[32,33]

An FDA analysis of the data also showed somewhat lower efficacy than the calculation by Novo Nordisk. However, and the unmet need for more drugs to treat obesity was taken into consideration as informing their decision to approve liraglutide.[34]

Liraglutide appears to be more effective in promoting weight loss than either orlistat or placebo. Evidence form the studies suggest that once the drug is withdrawn, weight loss may not be maintained.

It has been suggested that there is a lack of data to demonstrate improvement in cardiovascular outcomes and the sustainability of weight loss and glucose control in the long term.[2]

A systematic review of treatments available for obesity in the USA (orlistat, locaserin, and phenteramine plus topiramate) which did not include GLP-1 agonists concluded that medications for long term obesity treatment as an adjunct to lifestyle intervention may lead to greater mean weight loss relative to placebo. It also concluded that by discontinuing medication in patients who did not achieve at least 5% weight loss, patient exposure to risks and cost of drug treatment can be decreased when there is little prospect of long term benefit.[35]

Contraindications and precautions

Hypersensitivity to liraglutide or to any of the excipients.[13]

In patients with diabetes, liraglutide must not be used as a substitute for insulin.

There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II, and liraglutide should therefore be used with caution.

There is no experience in patients with congestive heart failure NYHA class III-IV and liraglutide is therefore not recommended in these patients.[13]

The safety and efficacy of liraglutide for weight management have not been established in patients:

- Aged 75 years or more,
- Treated with other products for weight management,
- With obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain,
- With severe renal impairment,
- With severe hepatic impairment.

Use in these patients is not recommended.[13]

As liraglutide for weight management was not investigated in subjects with mild or moderate hepatic impairment, it should be used with caution in these patients.[13]

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. Use of liraglutide is not recommended in these patients since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.[13]

Pancreatitis

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. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.[13]

Cholelithiasis and cholecystitis

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. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis.[13]

Thyroid disease

In clinical trials in T2DM, thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in particular in patients with pre-existing thyroid disease. Cases of increased blood calcitonin were also observed in the weight management clinical trials. Liraglutide should therefore be used with caution in patients with thyroid disease.[13]

Heart rate

An increase in heart rate was observed with liraglutide in clinical trials. The clinical significance of the heart rate elevation with liraglutide treatment is unclear, especially for patients with cardiac and cerebrovascular disease, as a result of limited exposure in these patients in clinical trials. Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should be informed of the symptoms of increased heart rate (palpitations or feelings of a racing heartbeat while at rest). For patients who experience a clinically relevant sustained increase in resting heart rate, treatment with liraglutide should be discontinued.[13]

Dehydration

Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with GLP-1 receptor agonists. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.[13]

Hypoglycaemia in patients with type 2 diabetes mellitus

Patients with T2DM receiving liraglutide in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea. The addition of liraglutide in patients treated with insulin has not been evaluated.[13]

The treatment effect has only been documented for one year. The need for continued treatment should be re-evaluated annually.[13]

Patients with type 2 diabetes mellitus

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

When initiating liraglutide, reducing the dose of concomitantly administered insulin or insulin secretagogues (e.g. sulfonylureas) should be considered to reduce the risk of hypoglycaemia.[13]

Special populations

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited and use in these patients is not recommended.[13]

Patients with renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance ≥30 mL/min). Liraglutide is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) including patients with end-stage renal disease.[13]

Patients with hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Liraglutide is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment.[13]

Paediatric population

The safety and efficacy of liraglutide in children and adolescents below 18 years of age have not been established. No data are available. This medicinal product is not recommended for use in paediatric patients.[13]

Safety and tolerability

GLP-1-based therapies may cause an increased heart rate and there have also been a small number of reports of acute pancreatitis, as well as gallstones and inflammation of the gallbladder.

These concerns will be closely monitored as part of the risk management plan for liraglutide.[11] In addition, safety monitoring for Saxenda® will also benefit from information that is collected for Victoza®

The FDA approval panel expressed concern about the lack of data beyond one year for liraglutide in obesity and a variety of safety issues including gallbladder disease, pancreatitis, breast and thyroid cancers, and increased heart rate although they were comfortable with those issues being addressed in postmarketing studies.[12]

In a review of the efficacy and safety of liraglutide for diabetes (lower doses than for weight loss), most common adverse effects were GI disturbance. During eight clinical studies with liraglutide, there were six cases of pancreatitis and five cases of cancer compared with one case each of pancreatitis in exenatide and glimepiride arms and one case of cancer in the metformin plus sitagliptin arm. Authors concluded that liraglutide was a new therapeutic option to improve glycaemic control in patients with T2DM. However the lack of evidence of durability of efficacy and long term safety appear to limit its utility in the treatment of T2DM at the time.[36]

Drug interactions

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.[13]

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption and therefore no dose adjustment is required.[13]

Interaction studies have been performed with 1.8mg liraglutide. The effect on rate of gastric emptying was equivalent between liraglutide 1.8mg and 3mg, (paracetamol AUC0-300 min). Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.[13]

Warfarin and other coumarin derivatives

No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR is recommended.[13]

Paracetamol (Acetaminophen)

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1,000 mg. Paracetamol Cmax was decreased by 31% and median tmax was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.[13]

Atorvastatin

Liraglutide did not change the overall exposure of atorvastatin following single dose administration of atorvastatin 40mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin Cmax was decreased by 38% and median tmax was delayed from 1h to 3h with liraglutide.[13]

Griseofulvin

Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500mg. Griseofulvin Cmax increased by 37% while median tmax did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are

not required.[13]

Digoxin

A single dose administration of digoxin 1mg with liraglutide resulted in a reduction of digoxin AUC by 16%; Cmax decreased by 31%. Digoxin median tmax was delayed from 1h to 1.5h. No dose adjustment of digoxin is required based on these results.[13]

Lisinopril

A single dose administration of lisinopril 20mg with liraglutide resulted in a reduction of lisinopril AUC by 15%; Cmax decreased by 27%. Lisinopril median tmax was delayed from 6h to 8h with liraglutide. No dose adjustment of lisinopril is required based on these results. [13]

Oral contraceptives

Liraglutide lowered ethinylestradiol and levonorgestrel Cmax by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product tmax was delayed by 1.5h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide. [13]

Pregnancy and lactation

Pregnancy

There are limited data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. [13] Liraglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide should be discontinued. [13]

Breast-feeding

It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Non-clinical studies have shown a treatment related reduction of neonatal growth in suckling rat pups Because of lack of experience, Saxenda should not be used during breast-feeding.[13]

Fertility

Apart from a slight decrease in the number of live implants, animal studies did not indicate harmful effects with respect to fertility. [13]

Costs/Tariff status/Activity costs

Comparative costs (BNF and Drug Tariff December 2015).

It is not possible to provide comparative costs at this stage.

Indication	Dose and frequency	Cost	Cost/28 days
Orlistat	120mg t.d.s.	£25.65/84	£25.65

Liraglutide is currently marketed as Victoza® for the treatment of T2DM. 2 x 3ml (6mg/ml) prefilled pens currently costs £78.48. The equivalent cost for one 3mg dose is therefore £6.54. Therefore treatment with 3mg once daily for 28 days would cost £183.12. The cost of Saxenda® is yet to be determined and there is currently no guarantee that the pricing of will be equivalent to Victoza®.

Cost effectiveness (if available)

Details unavailable.

Impact per 100,000 population/Affordability/Considerations

It is currently difficult to assess the impact per 100,000 population.

Following granting of the marketing authorisation, a decision about price and reimbursement will need take place considering the potential role/use of this medicine in the context of the NHS.

As the incidence of obesity is significant, (24% of males and 26% of females were classified as obese in 2011) the NHS may need to consider affordability in the context of the overall management of obesity.

It is most likely that if recommended for use in obesity, similar restrictive criteria would be applied as for orlistat and within the licensed indication.

Decisions from other bodies

SMC: Non identified.

AWMSG: Non identified

NICE: Non identified

Comments sought from

Local diabetologists/ obesity service consultants via PAC members

Evidence strengths and limitations

The efficacy of liraglutide 3mg daily has been demonstrated against placebo and orlistat for one year in the Phase III studies with a small number of patients receiving the 3mg dose for up to two years in the Phase II study.

There is a lack of data to suggest improvement in cardiovascular outcomes and the sustainability of weight loss and glucose control in the long term. There are also concerns regarding increased risk of pancreatitis, effects on the gall bladder, thyroid tumours and potential effects on heart rate.

There is also lack of data to demonstrate beneficial impact on wider outcomes including hospital admissions and potential impact on public health.

Options considered by PAC

Option 1. Liraglutide recommended in line with licensed indications and if patient meets eligibility criteria.

Option 2. Treatment of obesity with liraglutide is NOT recommended because of insufficient evidence in relation to long term efficacy and long term safety and because of specific safety concerns regarding serious adverse effects including pancreatitis.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

***Consult Summary of Prescribing Characteristics for full prescribing details.**

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Author: Melanie Whittick on behalf of PAC

Document history

PAC approval date	12th October 2015
Consultation process	PAC members and Consultant Diabetologists / Endocrinologists working in obesity services in the East of England

Version	v1
QA process	Katie Smith, Regional Medicines Information Director, East Anglia Medicines Information Service, 1st December 2015

References

1. National Institute for Health and Clinical Excellence. Obesity: Guidance on the prevention of overweight and obesity in adults and children. NICE guidelines [CG43] Published December 2006. https://www.nice.org.uk/guidance/cg43
2. National Institute for Health Research. Liraglutide for obesity or overweight in patients with associated comorbidities. Summary NIHR HSC ID: 7199. Horizon Scanning Centre University of Birmingham September 2013.
3. Scottish Intercollegiate Guidelines Network. Management of obesity. National Clinical Guideline 115. Edinburgh: SIGN; February 2010. http://www.sign.ac.uk/guidelines/fulltext/115/
4. Kim SH et al. Benefits of Liraglutide Treatment in Overweight and Obese Older Individuals With Prediabetes. American Diabetes Association. Diabetes Care 2013; 36 (10):3276-3282. http://www.ncbi.nlm.nih.gov/pubmed/23835684
5. Cochrane Library. The Central Register of Controlled Trials (CENTRAL) 2014 Issue 10. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/822/CN-00958822/frame.html Accessed 31st May 2015.
6. Vilsbøll T, Christensen M, Junker AE al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771
7. Sun F, Chai S, Li L, et al. Effects of Glucagon-Like Peptide-1 Receptor Agonists on Weight Loss in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. Journal of Diabetes Research 2015, Article ID 157201, 9 pages. http://dx.doi.org/10.1155/20125/157201
8. Van Gaal L, Scheen A. Weight Management in Type 2 Diabetes: Current and Emerging Approaches to Treatment. Diabetes Care 2015; 38 (6): 1161-1172. http://care.diabetesjournals.org/content/38/6/1161.full
9. Summary of Product Characteristics. Victoza. Novo Nordisk Limited, England, last updated 20 March 2013. http://www.medicines.org.uk/emc/medicine/21986/ Accessed 25/05/2015.
10. National Institute for Health and Clinical Excellence. Liraglutide for the treatment of type 2 diabetes mellitus. Technology appraisal TA203. London: NICE; October 2010.
11. European Medicines Agency. EMA/42196/2015. Press Office Press release. Saxenda recommended for approval in weight management in adults. Medicine to be used in addition to reduced-calorie diet and physical activity. 23 January 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/01/news_detail_002255.jsp&mid=WC0b01ac058004d5c1
12. The U.S. Food and Drug Administration. FDA News Release. FDA approves weight-management drug Saxenda. December 23, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm
13. Summary of Product Characteristics. Saxenda 6mg/ml solution for injection in pre-filled pen. Novo Nordisk AS. Accessed 25/05/15 via http://ec.europa.eu/health/documents/community-register/2015/20150323131125/anx_131125_en.pdf
14. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press; May 2015. Accessed 25/05/15 via https://www.evidence.nhs.uk/

formulary/bnf/current/4-central-nervous-system/45-drugs-used-in-the-treatment-of-obesity

15. National Institute for Health and Clinical Excellence. Obesity: identification, assessment and management of overweight and obesity in children, young people and adults. NICE guidelines [CG189] Published November 2014. https://www.nice.org.uk/guidance/cg189
16. European Medicines Agency MA/787060/2014 Press release Mysimba recommended for approval in weight management in adults Medicine to be used in addition to reduced-calorie diet and physical activity. 19 December 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/12/WC500179334.pdf
17. NICE technology appraisal in development. Phentermine with topiramate for the treatment of obesity and overweight (ID543). Suspended April 2013. https://www.nice.org.uk/guidance/indevelopment/gid-tag420 Accessed 27/05/15.
18. NICE technology appraisal in development. Lorcaserin hydrochloride for the treatment of obesity and overweight (ID337). Suspended May 2013. https://www.nice.org.uk/guidance/indevelopment/gid-tag439 Accessed 27/05/15.
19. National Institute for Health and Clinical Excellence. Managing overweight and obesity in adults – lifestyle weight management services. NICE guidelines [PH53] Published May 2014.
20. National Institute for Health and Clinical Excellence. Maintaining a healthy weight and preventing excess weight gain among adults and children. NICE guidelines [NG7] Published March 2015.
21. Astrup A, Rossner S, Van Gaal L et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009; 374 (9701):1606-16.
22. ClinicalTrials.gov. The Effect of Liraglutide on Body Weight in Obese Subjects Without Diabetes. https://clinicaltrials.gov/ct2/show/results/NCT00422058?sect=X70156#outcome1 Last verified April 2015. Accessed 29/05/15.
23. Astrup A et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes 2012;36 (6): 843-54.
24. ClinicalTrials.gov. Effect of LIraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALETM – Obesity and Pre-diabetes. https://clinicaltrials.gov/ct2/show/results/NCT01272219?sect=Xb70156#outcome5 Last verified 5 March 2015. Accesed 29/05/15
25. O'Neil et al. Efficacy and Safety of Liraglutide 3 mg in Adult Overweight and Obese Weight Loss responders without Diabetes: Results of the Randomised, Double Blind, Placebo-Controlled 56-Week Scale Obesity and Prediabetes Trial. Endocrine Society's 97th Annual Meeting. San Diego, California. 7 March 2015. https://endo.confex.com/endo/2015endo/webprogram/Paper19545.html?fromsource=nelm Accessed 29/05/15
26. ClinicalTrials.gov. Effect of Liraglutide on Body Weight in Overweight or Obese Subjects with Type 2 Diabetes. SCALETM – Diabetes. Last Verified 7 April 2015 https://clinicaltrials.gov/ct2/show/results/NCT01272232?sect=X01256#all Accessed 29/05/15
27. SCALE Diabetes: Continually Dosed Liraglutide May Aid Weight Loss in T2DM. Presented by: Ralph A. DeFronzo; Article written by: Lynne Lederman. European Association for the Study of Diabetes: 50th Annual Meeting - Published in November 2014. https://clinicaltrials.gov/ct2/show/study/NCT01272232?sect=X01256
28. ClinicalTrials.gov. Comparison of Liraglutide Versus Placebo in Weight Loss Maintenance in Obese Subjects: SCALETM – Maintenance. Last verified: April 2015. https://clinicaltrials.gov/ct2/show/results/NCT00781937 Accessed 29/05/15

29. Wadden TA, Hollander P, Klein S et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes 2013; 37(11):1443-51.

30. ClinicalTrials.gov. Effect of Liraglutide in Obese Subjects with Moderate or Severe Obstructive Sleep Apnoea: SCALETM – Sleep Apnoea. Last verified February 2015 https://clinicaltrials.gov/ct2/show/results/NCT01557166?sect=X870156&term=Liraglutide+AND+Apnoea&rank=1#outcome2 Accessed 29/05/15

31. Collier A, Blackman A, Foster G et al. S28 Liraglutide 3mg reduces Severity of Sleep Apnoea and Body Weight in Obese Individuals with Moderate or Severe Disease: Scale Apnoea Trial. Thorax 2014; 69: A16-A17 http://thorax.bmj.com/content/69/Suppl_2/A16.2 Accessed 29/05/15.

32. European Medicines Agency EPAR Summary for the Public EMA/197617/2015 EMEA/H/C/003780http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003780/WC500185789.pdf Accessed 30/05/15

33. Committee for Medicinal Products for Human Use (CHMP) EMA/143005/2015. Assessment Report Saxenda Procedure No. EMEA/H/C/003780/000 11 February 2015 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003780/WC500185788.pdf Accessed 30/05/15

34. Tucker ME. FDA Panel Endorses Liraglutide as Obesity Treatment. Medscape Medical News. September 12, 2014 http://thorax.bmj.com/content/69/Suppl_2/A16.2 Accessed 30/05/15

35. Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity. A Systematic and Clinical Review. JAMA 2014; 311 (1): 74-86.

36. Jeong KH, Yoo BK. The efficacy and safety of liraglutide. International Journal of Clinical Pharmacy 2011; 33 (5): 740-749.

Appendix 1- Search Strategy

Search History:

1. Medline; liraglutide.ti,ab; 837 results.

2. Medline; Obes*.ti,ab; 191533 results.

3. Medline; Overweight.ti,ab; 41418 results.

4. Medline; 2 OR 3; 203430 results.

5. Medline; 1 AND 4; 170 results.

6. Medline; 5 [Limit to: (Language English) and Humans]; 95 results.

7. EMBASE; liraglutide.ti,ab; 1862 results.

8. EMBASE; Obes*.ti,ab; 268066 results.

9. EMBASE; Overweight.ti,ab; 60322 results.

10. EMBASE; 8 OR 9; 283758 results.

11. EMBASE; 7 AND 10; 365 results.

Assessment against ethical and commissioning principles

Treatment assessed (May 2015)	**Liraglutide (Saxenda®) for obesity** 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. East of England Priorities Advisory Committee Recommendation - TBC
1. Clinical effectiveness	The effectiveness of liraglutide (Saxenda®) was shown in five clinical trials involving over 5,800 obese or overweight patients. All patients also received counselling on diet and physical activity.[11] Primary outcomes were change from baseline body weight and proportion of subjects losing ≥ 5%, and ≥ 10% in body weight. Looking at the results of the five studies together, liraglutide at a daily dose of 3mg led to a 7.5% reduction in body weight, compared with a 2.3% reduction in patients taking placebo. Patients treated with liraglutide had a continuous decrease in body weight during the first 40 weeks of treatment, after which the weight loss achieved was maintained.[32,33] When the figures for the main studies were re-analysed using a more conservative method that assumed that patients who did not complete the studies (around 30%) would not have seen any improvement, similar but smaller weight reductions with liraglutide were noted.[32,33] An FDA analysis of the data also showed somewhat lower efficacy than the calculation by Novo Nordisk. However, and the unmet need for more drugs to treat obesity was taken into consideration as informing their decision to approve liraglutide.[34] Liraglutide appears to be more effective in promoting weight loss than either orlistat or placebo. Evidence form the studies suggest that once the drug is withdrawn, weight loss may not be maintained.
2. Cost effectiveness	There is very limited cost effectiveness data.
3. Equity	No issues identified.
4. Needs of the community	It is difficult to assess the impact per 100,000 population. Being overweight and obese represent a rapidly growing threat to the health of populations globally. Obesity is a risk factor for coronary heart disease, hypertension and stroke, T2DM, certain cancers, dyslipidaemia, osteoarthritis, gout. The approach to preventing and managing obesity is multifaceted. Treatments include weight management programmes (i.e. dietary advice and weight loss targets, physical activity programmes, behavioural interventions and psychological support), pharmacological therapy and surgery. Pharmacological therapy should only be considered for patients who have already attempted to lose weight through weight management programmes. People with obesity and associated comorbidities including T2DM may utilise NHS resources in the management of obesity itself and associated conditions. The current lack of data on cost and cost effectiveness means that it is not possible to calculate the impact of funding this treatment, or to assess the potential need for disinvestment in other treatment areas.

5. Need for healthcare (incorporates patient choice and exceptional need)	Obesity may be considered as a disease and a risk factor for several other diseases (e.g. type 2 diabetes). In diagnosis of obesity the body mass index (BMI) is frequently used as a measure of overweight and obesity, with overweight being defined as a BMI 25-29.9kg/m^2 and obesity as a BMI ≥ 30kg/m^2. Unless the underlying problems both at population level and individual level (including lifestyle measures) are addressed effectively, obesity will continue to be a problem which needs to be approached by using multifaceted interventions. Pharmacological intervention alone will not address the underlying clinical problem for individuals. Pharmacological therapy should only ever be considered for patients who have already attempted to lose weight through weight management programmes. Obesity can result in several illnesses which may pose a significant risk to health and result in multiple readmissions. The overall cost to the NHS is unclear although there is a major impact on utilisation of resources.
6. Policy drivers	None.
7. Disinvestment	None identified. It is likely that this treatment (if approved) would be used in addition to current treatments.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*