Liraglutide for weight management in obese adolescents aged 12-17 years old

| NIHRIIO ID | 24082 | NICE ID | 10008 |
| Developer/Company | Novo Nordisk Ltd | UKPS ID | Not available |

Licensing and market availability plans | Currently in phase III clinical trials.

**SUMMARY**

Liraglutide is in development for weight management in obese adolescents aged 12-17 years old. Obesity is defined as abnormal or excessive fat accumulation that may impair health. Obesity is associated with an increased risk of a number of common causes of disease and death including diabetes, cardiovascular disease, and some cancers. For individuals classified as obese, the risk of poor health increases sharply with increasing Body Mass Index (BMI). The BMI is used to determine a person’s weight in regard to their height as underweight, of normal weight, overweight or obese. Preventing and managing obesity is a complex problem, and it is unlikely that obesity can be addressed through primary care management alone.

Liraglutide acts like a hormone the body produces naturally that regulates appetite, known as glucagon-like-peptide (GLP-1). By activating areas of the brain that regulate appetite, liraglutide may decrease feelings of hunger which can lead to lower calorie intake and weight loss. If licensed, liraglutide may improve long-term outcomes for weight management in obese adolescents 12-17 years old who currently have limited treatment options.
PROPOSED INDICATION

Weight management in obese adolescents aged 12-17 years old

TECHNOLOGY

DESCRIPTION

Liraglutide (Saxenda; Victoza) is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R). GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide, via specific activation of the GLP-1R, increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

Liraglutide is in clinical development for the weight management of adolescents with obesity. In the phase III clinical trial (NCT02918279), subjects 12-17 years old receive liraglutide at a concentration of 6 mg/mL solution for injection administered once daily subcutaneously for 56 weeks.

INNOVATION AND/OR ADVANTAGES

Lifestyle and behavioral interventions remain the mainstream of the obesity treatment in children, but adjunctive pharmacotherapy may be beneficial in some patients. Data derived from adults suggest that pharmacological therapy as an adjunct therapy might offer benefits for those patients who fail to respond to lifestyle modification alone. Over the last years medications approved to treat obesity in adults has increased, but most of these drugs are not licensed for the treatment of obesity in children and adolescents.

Liraglutide helps to induce and sustain weight loss in patients with obesity. Its efficacy is comparable to other available agents but it offers the unique benefit of improved glycemic control. Recent short-term studies in paediatric subjects have confirmed that the tolerability, efficacy and safety of liraglutide are similar to adults. The results suggest that the approved dose for weight management in adults may be appropriate even in adolescents. Early identification, during childhood, of individuals who most likely respond favorably to a specific anti-obesity agent will be possibly more efficacious in addressing the global obesity epidemic, than pharmacotherapies started in older ages.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Liraglutide (Saxenda) is indicated in the EU/UK 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:
- \( \geq 30 \text{ kg/m}^2 \) (obese), or
- \( \geq 27 \text{ kg/m}^2 \) to \(<30 \text{ kg/m}^2 \) (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus [T2DM]), hypertension, dyslipidaemia or obstructive sleep apnoea.
Liraglutide (Victoza) is indicated in the EU/UK for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise: 7

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications;
- in addition to other medicinal products for the treatment of diabetes.

Very common (≥1/10) adverse effects of liraglutide may include nausea, vomiting, diarrhoea, and constipation. 2,7 Liraglutide is in phase III clinical development for paediatric Prader-Willi Syndrome, polycystic ovary syndrome, and a number of other metabolism and nutrition disorders including pre-diabetes, binge-eating disorder, gestational diabetes, metabolic syndrome and others. 8

PATIENT GROUP

DISEASE BACKGROUND

 Obesity is a condition in which abnormal or excessive fat accumulation in adipose tissue impairs health. In most cases, it is the result of energy intake exceeding energy expenditure over a period of years. 9 The most widely used measure of obesity is the Body Mass Index (BMI), defined as weight divided by the square of height (kg/m²). 10

In children and adolescents, BMI should be used as a practical estimation of body fat. Assessing the BMI of children is more complicated than for adults because it changes as they grow and mature. In addition, growth patterns differ between boys and girls. Thresholds that take into account a child’s age and sex are used to assess whether their BMI is too high or too low. These are usually derived from a reference population, known as a child growth reference, with the data presented in BMI centile charts. In a clinical assessment, a child or young person on or above the 98th centile is classified as obese. A child or young person on or above the 91st centile, but below the 98th centile, is classified as overweight. 11

It is well recognised that children who are obese are likely to have obese parents. Obesity that runs in families can be due to environmental factors (such as poor eating habits learned during childhood), or due to relational and behavioural factors (such as poor boundary setting), as well as certain genetic traits being inherited from parents. 12 There is also a strong relationship between deprivation and overweight/obesity prevalence. In 2015/2016, 40% of children in England’s most deprived areas were overweight or obese, compared to 27% in the most affluent areas. 13

Up to 79% of children who are obese in their teens are likely to remain obese as adults. This can lead to health problems in adulthood such as type 2 diabetes, heart disease and certain cancers. Various diseases or conditions may be associated with obesity in children. Type 2 diabetes, a condition previously found almost entirely in adults, is now being diagnosed in children and young people. Being overweight as a child can also impact on self-esteem and quality of life, and cause depression. 12

Treating children for overweight or obesity may stigmatise them and put them at risk of bullying, which in turn can aggravate problem eating. 14 Confidentiality and building self-esteem are particularly important if help is offered at school. 12

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, as with other high-income English-speaking countries, the rise in childhood obesity seems to have stabilized in the past decade, albeit at high levels. A 2017 study pooling information for children aged 5 to 19 years reported approximately 10% of UK children to be obese. Obesity in boys rose from 2.4% in 1975 to 10.9% in 2016, while obesity in girls rose from 3% in 1975 to 9.4% in 2016.
At the time of publication, the UK ranked 73rd on the Non-Communicable Diseases (NCD) Risk Factor Collaboration list of 200 countries for childhood obesity prevalence.\textsuperscript{15,16} By 2020 it is estimated half of all children in the UK will be overweight or obese.\textsuperscript{13}

In 2017, the Health Survey for England (HSE) found 30% of children aged 2 to 15 in England were overweight or obese, including 17% who were obese. Boys and girls were equally likely to be overweight or obese. The HSE also found 28% of children of obese mothers were also obese, compared to with 17% of children whose mothers were overweight but not obese and 8% of children whose mothers were neither overweight nor obese and 24% of children of obese fathers were themselves obese, compared with 14% of children whose fathers were overweight but not obese, and 9% of children whose fathers were neither overweight nor obese.\textsuperscript{17}

Analysis of HSE data from 2006 to 2013 on obese children and young people aged 2-18 suggest 11.2% (1.22 million) were eligible for primary care assessment for community lifestyle modification. Among those aged 13-18 years, 8.2% (309,000) were eligible for anti-obesity drug therapy and 2.4% (90,500) were eligible for bariatric surgery. Children and young people from the most deprived quintile were 1.5-3 times more likely to be eligible for obesity management.\textsuperscript{18}

It was estimated that the NHS in England spent £6.1 billion on overweight and obesity-related ill-health in 2017/18.\textsuperscript{19} The burden of child and adolescent obesity within NHS England is unclear due to available data on service use in England, particularly among deprived young people.\textsuperscript{18} In 2017/18 NHS England recorded a total of 2,590 diagnoses of obesity (E66) for age 10-14, 776 for age 15, 962 for age 16, and 1,495 for age 17.\textsuperscript{20}

### PATIENT TREATMENT PATHWAY

#### TREATMENT PATHWAY

NICE recommends the following in the identification, assessment and management of obesity in children (aged 2 years and over) and young people:\textsuperscript{21}

- **Use BMI (adjusted for age and gender) as a practical estimate of adiposity in children and young people.** BMI should be interpreted with caution as it is not a direct measure of adiposity. Waist circumference is not recommended as a routine measure in children.

- **Lifestyle interventions:** Multicomponent interventions are the treatment of choice. Ensure weight management programmes include behaviour change strategies to increase physical activity levels or decrease inactivity, improve eating behaviour and the quality of the person’s diet, and reduce energy intake. The aim of weight management programmes for children and young people can vary. The focus may be on either weight maintenance or weight loss, depending on the person’s age and stage of growth.

- **Behavioural interventions:** Deliver any behavioural intervention with the support of an appropriately trained professional. Including the following strategies in behavioural interventions for children, as appropriate: stimulus control, self-monitoring, goal setting, rewards for reaching goals, and problem solving. Give praise to successes and encourage parents to role-model desired behaviours.

- **Physical activity:** Encourage children and young people to increase their level of physical activity, even if they do not lose weight as a result, because of the other health benefits exercise can bring. Encourage children to do at least 60 minutes of moderate or greater intensity physical activity each day. The activity can be in 1 session or several sessions lasting 10 minutes or more.
Encourage children to reduce inactive behaviours while incorporate more exercise in their daily lives and through regular, structured physical activity.

- **Dietary:** A dietary approach alone is not recommended. It is essential that any dietary recommendations are part of a multicomponent intervention. Any dietary changes should be age appropriate and consistent with healthy eating advice. For overweight and obese children and young people, total energy intake should be below their energy expenditure. Changes should be sustainable.

- **Surgical intervention is not generally recommended in children or young people. Bariatric surgery may be considered for young people only in exceptional circumstances, and if they have achieved or nearly achieved physiological maturity. Surgery for obesity should be undertaken only by a multidisciplinary team that can provide paediatric expertise.**

### CURRENT TREATMENT OPTIONS

In children aged 12 years and older, treatment with orlistat is recommended only if physical comorbidities (such as orthopaedic problems or sleep apnoea) or severe psychological comorbidities are present. Treatment should be started in a specialist paediatric setting, by multidisciplinary teams with experience of prescribing in this age group.\(^{21}\)

### PLACE OF TECHNOLOGY

If licensed, liraglutide will offer an additional treatment option for weight management in obese 12-17 year olds who currently have few effective therapies available.

### CLINICAL TRIAL INFORMATION

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02918279, EuraCT2014-004353-14; children aged 12-17 years; liraglutide vs placebo; phase III</th>
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<td>Sponsor</td>
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<td>Novo Nordisk A/S</td>
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<td>Status</td>
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<td>Ongoing</td>
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<td>Source of Information</td>
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<td>Trial registry(^1)(^3)</td>
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<td>2 EU countries (not UK), USA, Mexico and Russia</td>
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<tr>
<td>Design</td>
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<td>Randomised, parallel assignment, double-blind, placebo-controlled</td>
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<td>Participants</td>
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<td>n=228 (planned); male or female, age 12 to less than 18 years at the time of signing informed consent and less than 18 years at date of randomisation; BMI corresponding (\geq 30) kg/m(^2) for adults by international cut-off points and (\geq 95)th percentile for age and sex (for diagnosis of obesity); stable body weight during the previous 90 days before screening V2 (below 5 kg self-reported weight change); history of failing to lose sufficient weight with lifestyle modification</td>
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<td>Schedule</td>
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<td>Subjects in the experimental arm receive liraglutide at a concentration of 6 mg/mL solution for injection administered once daily subcutaneously for 56 weeks.</td>
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<td>Follow-up</td>
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<td>Active treatment for 56 weeks, followed by a 26-week period off study-drug</td>
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<td>Primary Outcomes</td>
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<td>Change in BMI standard deviation score [Time frame: week 0, week 56]</td>
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<td>Secondary Outcomes</td>
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<td>Time frame: at week 56</td>
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- Percent of subjects achieving equal to or above 5% reduction in baseline BMI
- Percent of subjects achieving equal to or above 10% reduction in baseline BMI

**Time frame: week 0, week 56**
- Change in BMI
- Change in body weight (kilogram [kg], pounds [lb])
- Change in body weight (percent [%])
- Change in systolic and diastolic blood pressure
- Change in glucose metabolism: glycosylated haemoglobin (HbA1c)
- Change in fasting plasma glucose
- Change in number of treatment emergent adverse events

**Key Results**

**Adverse effects (AEs)**

**Expected reporting date** Study estimated completion date reported as Aug 2019.

### ESTIMATED COST

Liraglutide is already marketed in the UK; x 5 pre-filled disposable injection pen of Saxenda 6 mg/mL costs £196.20, x 2 Victoza 6 mg/mL pre-filled disposable injection pen costs £78.48 (drug tariff - Part VIII A Category C), and x 3 Victoza 6 mg/mL pre-filled disposable injection pen costs £117.72.\(^2\)

### ADDITIONAL INFORMATION

Novo Nordisk Ltd declined to provide comments.

Novo Nordisk Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

### RELEVANT GUIDANCE

**NICE GUIDANCE**


NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

OTHER GUIDANCE
• The European Society of Endocrinology and the Pediatric Endocrine Society. Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. 2017

REFERENCES


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