December 2018

New Medicine Assessment
Semaglutide (Ozempic®▼)
Treatment of Adults with Insufficiently Controlled Type 2 Diabetes

Recommendation: GREEN

Semaglutide is an appropriate treatment option for initiation and ongoing prescribing in both primary and secondary care when prescribed in the following clinical circumstances:

- after second intensification of therapy fails to achieve targets*****:
    - has a BMI of ≥35 kg/m^2 and specific psychological or other medical problems associated with obesity (adjust accordingly for people from Black, Asian and other minority ethnic groups) or
    - has a BMI < 35 kg/m^2 and
        - if insulin therapy would have significant occupational implications or
        - if weight loss would benefit other significant obesity related comorbidities

Or, with specialist care advice and ongoing support from a consultant-led multidisciplinary team:

- combined with insulin at second intensification of treatment in patients who cannot take metformin

Semaglutide may only be continued if the person has a beneficial metabolic response, defined as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] and
- a weight loss of at least 3% of initial body weight in 6 months

*** Wording consistent with LMMG antihyperglycaemics guideline (semaglutide to be accommodated within the LMMG antihyperglycaemics guideline if proposed use within this New Medicine Recommendation is agreed)**

Summary of supporting evidence:

- The phase 3 clinical trials programme for semaglutide consistently demonstrated statistically significant reductions in HbA_{1c} and body weight.
- Semaglutide demonstrated statistically significant reductions in HbA_{1c} and body weight in comparison to exenatide and dulaglutide.
- The acquisition cost of semaglutide is equal to that of dulaglutide (and lowest dose of liraglutide), and less than the acquisition cost of daily/weekly exenatide and maximal dose liraglutide.
- Semaglutide is a once-weekly injection which may be simpler and more convenient for patients than once/twice daily GLP-1 receptor agonists.
- The cardiovascular outcome trial (SUSTAIN 6) showed a statistically significant 26% reduction in risk of a composite of non-fatal stroke, non-fatal myocardial infarction (MI), cardiovascular death and time to first occurrence of major adverse cardiovascular event in patients treated with semaglutide. The study however did not show reductions in cardiovascular death which the EMA consider to be more clinically relevant than non-fatal MI and non-fatal stroke.
- The EMA concluded that a persistent deleterious effect of semaglutide on the retina independent of rapid glucose lowering cannot be excluded.

Details of Review

Name of medicine (generic & brand name)**:**

Semaglutide (Ozempic®).

Strength(s) and form(s):

0.25 mg, 0.5mg and 1mg solution for injection pre-filled pens. (one ml of solution contains 1.34 mg of Semaglutide).

Dose and administration:

The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 1 mg are not recommended.

BNF therapeutic class / mode of action:

Glucagon-like-peptide-1 (GLP-1) receptor agonists/ Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Licensed indication(s):

Semaglutide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

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

Proposed use (if different from, or in addition to, licensed indication above):

As an option at first line in the LMMG antihyperglycaemics guideline.

Course and cost:

All strengths - Four weeks treatment = £73.25, annual cost = £954.86

Current standard of care/comparator therapies:

- Dulaglutide (Trulicity®) - Four weeks treatment = £73.25, annual cost = £954.86
- Exenatide (Bydureon®) – Four weeks treatment = £73.36, annual cost = £956.30
- Liraglutide (Victoza®) – 30 days treatment = £78.48 – £117.72, annual cost = £954.84 - £1,432.26
- Exenatide (Byetta®) – 30 days treatment = £81.89, annual cost = £996.33
- Lixisenatide (Lyxumia®) – 28 days treatment = £57.93, annual cost = £755.16

Relevant NICE guidance:

NICE guideline (NG28) – Type 2 diabetes in adults: management. [1]
1.6.28 If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
    - for whom insulin therapy would have significant occupational implications **or**
    - weight loss would benefit other significant obesity-related comorbidities.

1.6.29 Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months).

1.6.31 In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

Background and context

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. [1]

In 2013, over 3.2 million adults were diagnosed with diabetes, with prevalence rates of 6% and 6.7% in England and Wales respectively. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family origin. It can occur in all age groups and is increasingly being diagnosed in children. [1]

GLP-1 receptor agonists are used in type 2 patients whose HbA_{1c} remains uncontrolled despite the use of triple therapy oral antihyperglycaemic agents. Currently Lancashire Medicines Management Group recommends weekly dulaglutide/exenatide (Bydureon®) as first line GLP-1 receptor agonists and liraglutide as a second line agent where there is clinician/patient preference for the use of a daily GLP-1 receptor agonist. [2]

Summary of evidence

Summary of efficacy data in proposed use:

Seven published phase III trials (SUSTAIN trials 1-7 [3] [4] [5] [6] [7] [8] [9]) evaluated the efficacy and safety of semaglutide in patients with type 2 diabetes. The clinical trials assessed semaglutide as either a monotherapy or in combination with other oral antidiabetic agents. SUSTAIN 6 was a long term cardiovascular outcomes trial in type 2 patients at high risk of cardiovascular events. [8]

The SUSTAIN trials which are most relevant to the proposed use have been included in this section of the New Medicine Recommendation, the remaining trials are included in the other efficacy data section (below).

SUSTAIN 7 and SUSTAIN 3 studies

These international, open-label studies compared semaglutide with dulaglutide (SUSTAIN 7) and with exenatide extended-release (SUSTAIN 3). Patients enrolled were ≥ 18 years, with type 2 diabetes and HbA_{1c} of 7.0–10.5% (53.0–91.0 mmol/mol) and on stable diabetes treatment for ≥ 90 days before screening. Patients in SUSTAIN 7 were receiving metformin at a minimum dose of 1,500 mg/day or a maximal tolerated dose. Patients in SUSTAIN 3 were receiving stable treatment with one or two oral antidiabetic medicines (metformin and/or a thiazolidinedione and/or a sulphonylurea). [5] [9]

Patients were excluded if they had a glomerular filtration rate < 60 ml/min/1.73 m^2 (chronic kidney disease stage 3), a history of pancreatitis, an acute coronary or cerebrovascular event within 90 days before randomisation, or heart failure (New York Heart Association class IV), or were receiving chronic treatment with glucose-lowering medicines (other than those in the inclusion criteria) within 90 days of screening. The SUSTAIN 7 study excluded patients with proliferative retinopathy or maculopathy requiring acute treatment. [10]

Patients in the SUSTAIN 7 study were randomly assigned to receive treatment once-weekly for 40 weeks with semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg or dulaglutide 1.5 mg. Patients in the SUSTAIN 3 study were randomised to once-weekly semaglutide 1.0 mg or once-weekly exenatide extended-release 2.0 mg for 56 weeks. In both studies, the semaglutide dose was escalated: patients received a starting dose of 0.25 mg which doubled every four weeks until the study maintenance dose was reached (0.5 mg or 1.0 mg in SUSTAIN 7; 1.0 mg in SUSTAIN 3). [10]

The primary endpoint was change in percentage HbA_{1c} from baseline to week 40 (SUSTAIN 7) or week 56 (SUSTAIN 3). The European Medicines Agency considered a pre-defined non-inferiority margin of ≥ 0.3% (3 mmol/mol) as acceptable for a clinically meaningful reduction in HbA_{1c} [11]. A confirmatory secondary endpoint was change in body weight from baseline to week 40 (SUSTAIN 7) or week 56 (SUSTAIN 3). Key results from the SUSTAIN 7 and SUSTAIN 3 studies are shown in Table 1. [10]

In the SUSTAIN 7 study, 1,199 patients were exposed to treatment and included in the efficacy and safety analyses. After 40 weeks of treatment, reductions in HbA_{1c} were statistically significantly greater in patients treated with semaglutide 1.0 mg (−1.8%) than those treated with dulaglutide 1.5 mg (−1.4%; $p < 0.0001$ for both non-inferiority and superiority). Patients treated with semaglutide 1.0 mg also lost significantly more weight than those treated with dulaglutide 1.5 mg (−6.5 kg versus −3.0 kg; $p < 0.0001$ for both non-inferiority and superiority) (see Table 1).

After 40 weeks most domains of the patient-reported outcome short-form health survey 36 version 2 questionnaire (SF-36v2) improved for both doses of semaglutide and dulaglutide, although the changes were not significantly different. Most items of the diabetes treatment satisfaction questionnaire had improved at Week 40 for both doses of semaglutide and dulaglutide. Patient perception of unacceptable hyperglycaemia significantly improved in semaglutide-treated patients compared with dulaglutide-treated patients. [10]

In the SUSTAIN 3 study, 809 patients were exposed to treatment and were included in the efficacy and safety analysis. Semaglutide showed superiority to exenatide extended-release in both the primary endpoint and confirmatory secondary endpoint. Patients treated with semaglutide for 56 weeks had a statistically significantly greater reduction in HbA_{1c} (−1.5%) compared with exenatide (−0.9%) and lost statistically significantly more weight (−5.6 kg compared with −1.9 kg). No significant differences between the treatment groups were seen for the domains assessed by the SF-36v2 health questionnaire. Patients treated with semaglutide had a significantly greater improvement in overall treatment satisfaction ($p = 0.0068$) and self-perceived hyperglycaemia ($p = 0.0200$) as measured by diabetes treatment satisfaction questionnaire scores (see Table 1).

SUSTAIN 5 study

This double-blind study enrolled 397 adults with type 2 diabetes who were randomised to receive either semaglutide (0.5 mg or 1.0 mg) or placebo (0.5 mg or 1.0 mg) once weekly for 30 weeks as an add-on to basal insulin with or without metformin. [16] As add-on to basal insulin, semaglutide was superior to placebo in reducing HbA_{1c} and body weight. More hypoglycaemic events were reported in the semaglutide groups compared with the placebo group (see Table 1).

Table 1. Key endpoints of the SUSTAIN 7, 3 and 5 studies [10]

SUSTAIN 7* (in adults taking metformin)	**Semaglutide 1.0 mg once weekly**	**Dulaglutide 1.5 mg once weekly**	**Treatment difference (95% CI)**	**p-value**
Change in HbA1c from baseline at week 40 (%) - final analysis set	−1.8 (0.06)	−1.4 (0.06)	−0.41 (−0.57 to −0.25)	<0.0001
Change in body weight at week 40 (kg)	−6.5 (0.28)	−3.0 (0.27)	−3.55 (−4.32 to −2.78)	<0.0001
SUSTAIN 3 (in adults taking one or two antidiabetic medicines)	**Semaglutide 1.0 mg once weekly**	**Exenatide ER 2.0 mg once weekly**		
Change in HbA1c from baseline at week 56 (%)	−1.5	−0.9	−0.62 (−0.80 to −0.44)	<0.0001
Change in body weight at week 56 (kg)	−5.6	−1.9	−3.78 (−4.58 to −2.98)	<0.0001
SUSTAIN 5 (in adults taking basal insulin with or without metformin)	**Semaglutide 1.0 mg once weekly**	**Placebo 1.0 mg**		
Change in HbA1c from baseline at week 30 (%)	−1.8	−0.1	−1.75 (−2.01 to −1.50)	<0.0001
Change in body weight at week 30 (kg)	−6.4	−1.4	−5.06 (−6.08 to −4.04)	<0.0001
* Full analysis set CI: confidence interval; ER: extended-release; HbA1c: glycated haemoglobin; SE standard error				

Other efficacy data:

The outcome measures for the additional SUSTAIN trials discussed below were similar to that described above for SUSTAIN 3 and 7 (change in percentage HbA_{1c} and change in body weight from baseline).

SUSTAIN 1

This was a 30 week, randomised, double-blind, parallel-group, placebo-controlled, multinational, multicentre, four-armed trial to evaluate the efficacy and safety of once-weekly semaglutide as monotherapy in adult subjects with type 2 diabetes. [3]

Findings from SUSTAIN 1 demonstrated significant reductions in HbA_{1c} compared to placebo (semaglutide 0.5 mg = -1.45% [CI 95% -1.71%, -1.15%] and semaglutide 1 mg = -1.53% [CI 95% -1.81, -1.25]). The study also demonstrated significant reductions in weight compared to placebo (semaglutide 0.5 mg = -2.75 kg [CI 95% -3.92, -1.58] and semaglutide 1 mg = -3.56 kg [CI 95% -4.74, -2.38]). [12]

SUSTAIN 2

This was a 56-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre, multinational, four-armed trial investigating the efficacy and safety of semaglutide 0.5 mg and 1.0 mg once-weekly versus sitagliptin 100 mg once-daily in subjects with type 2 diabetes who had not achieved adequate glycaemic control on metformin, thiazolidinedione or a

combination of metformin/thiazolidinedione. [4]

Results from this study showed significant reductions in HbA_{1c} compared to sitagliptin (semaglutide 0.5 mg = -0.77% [CI 95% -0.92%, -0.62%] and semaglutide 1 mg = -1.06% [CI 95% -1.21, -0.91]). The study also demonstrated significant reductions in weight compared to sitagliptin (semaglutide 0.5 mg = -2.35 kg [CI 95% -3.06, -1.63] and semaglutide 1 mg = -4.20 kg [CI 95% -4.91, -3.49]). [12]

SUSTAIN 4

This was a 30-week randomised, open-label, active-controlled, parallel-group, multicentre, multinational, three-armed trial comparing two doses of semaglutide (0.5 mg and 1.0 mg) once-weekly versus insulin glargine once-daily.

Findings from SUSTAIN 4 demonstrated significant reductions in HbA_{1c} compared to once daily insulin glargine (semaglutide 0.5 mg = -0.38% [CI 95% -0.52%, -0.24%] and semaglutide 1 mg = -0.81% [CI 95% -0.96, -0.67]). The study also demonstrated significant reductions in weight compared to insulin glargine (semaglutide 0.5 mg = -4.62 kg [CI 95% -5.27, -3.96] and semaglutide 1 mg = -6.33 kg [CI 95% -6.99, -5.67]). [12]

Network meta-analyses

Two meta-analyses have been published comparing semaglutide to the other marketed GLP-1 receptor agonists. [13] [14] In patients using a GLP-1 receptor agonist in combination with one or two antidiabetic drugs, a network meta-analysis of 26 studies demonstrated statistically greater reductions in HbA_{1c} and body weight at six months for semaglutide 1mg. [13] The second network meta-analysis of 8 studies comparing GLP-1 receptor agonists used in combination with basal insulin demonstrated similar results with semaglutide 1mg producing the greatest reduction in HbA_{1c} and body weight at six months. [14]

Summary of safety data:

According to the EPAR for semaglutide, eight completed phase 3 trials and a cardiovascular outcomes trial provided safety data relating to approximately 4,800 patients and over 5,600 patient years of exposure. [12] Additional safety data is also available from the SUSTAIN 7 which assessed semaglutide and dulaglutide. [9]

Adverse events

The EPAR states that “The safety profile of semaglutide is generally consistent with those reported for other drugs in the GLP-1 RA class”. The EMA noted that the rates of gastrointestinal adverse events were higher for semaglutide compared to exenatide, sitagliptin and insulin glargine. [12] However the open label SUSTAIN 7 study found that the frequency of gastrointestinal adverse effects were similar between semaglutide and dulaglutide groups. [9]

A significantly increased risk of diabetic retinopathy complications was observed with semaglutide as compared with placebo. This increased risk was particularly marked in patients with pre-existing diabetic retinopathy at baseline and co-use of insulin. Although it is recognised that intensified glycaemic control may precipitate early worsening of diabetic retinopathy, clinical trials data did not demonstrate a decrease in the risk of diabetic retinopathy over the course of two years, and data also suggests that semaglutide was associated with retinopathy in patients with only small HbA_{1c} reductions. [12] A specific warning has been included in the SPC for semaglutide outlining the increased risk of diabetic retinopathy complications in patients with existing diabetic retinopathy treated with insulin. [15]

The SPC for semaglutide lists the following adverse events [13]:

Table 2. Adverse reactions from long-term controlled phase 3a trials including the cardiovascular

outcomes trial.

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or sulfonylurea	Hypoglycaemia when used with other OADs Decreased appetite		
Nervous system disorders		Dizziness	Dysgeusia	
Eye disorders		Diabetic retinopathy complications		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence		
Hepatobiliary disorders		Cholelithiasis		
General disorders and administration site conditions		Fatigue	Injection site reactions	
Investigations		Increased lipase Increased amylase Weight decreased		

Contraindications, precautions and interactions

Semaglutide is contraindicated in patients with a hypersensitivity to the active substance or any of the product excipients. Semaglutide should not be used in pregnancy or lactation and women of child bearing age are recommended to use contraception when treated with semaglutide. [15]

The SPC includes warnings about gastrointestinal adverse effects such as diarrhoea and vomiting which may cause dehydration leading to deterioration of renal function. Patients should be warned about the characteristic symptoms of acute pancreatitis, particularly in patients with a history of pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued and if confirmed, semaglutide should not be restarted. The SPC also advises of the increased risk of hypoglycaemia in patients treated with semaglutide in combination with a sulfonylurea or insulin. Prescribers can reduce the risk of hypoglycaemia by the lowering the dose of sulfonylurea or insulin. [15]

Therapeutic experience in patients ≥75 years of age is limited. Semaglutide can be used in people with mild, moderate or severe renal impairment but it is not recommended for use in patients with end-stage renal disease. Experience with the use of semaglutide in patients with

severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide. [15]

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products that require rapid gastrointestinal absorption. Upon initiation of semaglutide treatment, it is recommended that patients on warfarin or other coumarin derivatives undertake frequent monitoring of their INR. [15]

SUSTAIN 6 cardiovascular study [8]

SUSTAIN 6 was a long-term, cardiovascular study of semaglutide as an add-on to standard of care (including insulin) in 3,297 patients with diabetes and established, or at high risk of, cardiovascular disease. [19] Results showed a statistically significant 26% reduction in risk of a composite of non-fatal stroke, non-fatal myocardial infarction (MI), cardiovascular death and time to first occurrence of major adverse cardiovascular event in patients treated with semaglutide for 104 weeks (hazard ratio 0.74; CI95% 0.58; 0.95, $p < 0.001$). [10] These results were driven by a reduction in non-fatal MI and non-fatal stroke. The results of SUSTAIN 6 did not demonstrate a beneficial or negative effect on either cardiovascular death or non-cardiovascular death.

Strengths and limitations of the evidence:

Strengths

- The phase 3 clinical trials programme for semaglutide consistently demonstrated statistically significant reductions in HbA_{1c} and body weight.
- Semaglutide demonstrated statistically significant reductions in HbA_{1c} and body weight in comparison to exenatide and dulaglutide.
- The cardiovascular outcomes trial (SUSTAIN 6) for semaglutide showed significant reductions in non-fatal MI and non-fatal stroke in the semaglutide group.
- Authors of the SUSTAIN 7 clinical trial concluded that the safety profile of semaglutide and dulaglutide were broadly similar.
- The risk of hypoglycaemia was not increased in patients using semaglutide (except when used in combination with insulin or sulfonylureas).
- The acquisition cost of semaglutide is equal to that of dulaglutide (and lowest dose of liraglutide), and less than the acquisition cost of daily/weekly exenatide and maximal dose liraglutide.
- Semaglutide is a once-weekly injection which may be simpler and more convenient for patients than once/twice daily GLP-1 receptor agonists.

Limitations

- The cardiovascular outcome trial (SUSTAIN 6) did not show reductions in cardiovascular death which the EMA consider to be more clinically relevant than the demonstrated non-fatal MI and non-fatal stroke.
- Hospitalisation for heart failure, all-cause mortality, serious adverse events (SAEs) of coronary artery disease, SAEs of cardiac failure and vascular therapeutic procedures (particularly cardiac interventions) were higher with semaglutide than with placebo in SUSTAIN 6.
- Generalisability of the cardiovascular outcome trial is limited, as the study enrolled only patients with a high cardiovascular risk.
- The EMA concluded that a persistent deleterious effect of semaglutide on the retina independent of rapid glucose lowering cannot be excluded.
- The SUSTAIN 3 and SUSTAIN 7 which compared semaglutide to exenatide and dulaglutide respectively were open label trials and showed relatively smaller reductions in HbA_{1c} and weight loss for exenatide and dulaglutide than were previously noted in the DURATION and AWARD trials (pivotal trials for exenatide and dulaglutide).

- In SUSTAIN 3 exenatide was administered using a vial and syringe, which differs from the pen-filled injection which would be used in practice. This may have impacted the results obtained for patients using exenatide in SUSTAIN 3.
- In SUSTAIN 7 patients were using either semaglutide or dulaglutide in combination with metformin ONLY. This is not in line with current practice as both current NICE guidance and the LMMG antihyperglycaemic guideline recommend GLP-1 mimetics following the use of triple therapy (metformin and two oral antidiabetic agents).
- Treatment discontinuations were more common in patients using semaglutide (15-17%) than patients using dulaglutide (9-12%) in the SUSTAIN 7 trials.

Summary of evidence on cost effectiveness:

A company submission to the All Wales Medicines Strategy Group included a cost-utility analysis of semaglutide 0.5 mg and 1 mg for once-weekly injection compared with other GLP-1 receptor agonists available in the UK. [10]

Results

Semaglutide 1 mg and 0.5 mg as part of dual and triple therapy and as an add-on to basal insulin is reported to produce small increases in Quality Adjusted Life years (QALYs) and slight cost savings and thus dominate all other GLP-1 receptor agonist treatment options available (in Wales) except lixisenatide where it is slightly more expensive but also more effective although remains cost effective.

Prescribing and risk management issues:

The licensed indications for semaglutide are much wider than the relatively restrictive settings in the LMMG antihyperglycaemics guideline. [1] [2] If semaglutide was approved for use across Lancashire and South Cumbria, its place would need to be defined in the LMMG antihyperglycaemics pathway.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost (£)	Cost per patient per course/ per year (ex VAT) (£)
Semaglutide 0.5 mg/1 mg pre-filled pen	**1 mg weekly**	**73.25**	954.86
Dulaglutide 750 mcg/1.5 mg pre-filled pen	1.5 mg weekly	73.25	954.86
Exenatide weekly (Bydureon) 2 mg pre-filled pen	2 mg weekly	73.36	956.30
Liraglutide 6 mg/ml pre-filled pen	1.2 mg-1.8 mg daily	78.48-117.72	954.84 - 1,432.26
Exenatide daily (Byetta) 10 mcg pre-filled pen	10 mcg twice daily	81.89	996.33
Lixisenatide 20 mcg pre-filled pen	20 mcg daily	57.93	755.16

Costs based on MIMS list prices October 2018.
This table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

Additional costs would be incurred for needle supply and disposal. Based on the similar safety

profile of semaglutide compared to the other GLP-1 receptor agonists, additional costs relating to adverse events are not anticipated.

Productivity, service delivery, implementation:

Patients will need to be taught how to use the injections and there will need to be arrangements for the safe disposal of sharps. The NICE Clinical Guideline 28 and LMMG guideline mandate specialist team input if GLP-1 drugs are to be used alongside insulin, stating:

"Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team".

Anticipated patient numbers and net budget impact:

Estimated budget impact assumptions used statistics taken from the Office for National statistics, Diabetes UK and NHS Digital. [16] [17] [18]

Total population of Lancashire and South Cumbria: **1,675,000** (Office for National Statistics)
Adult population (78.9%): **1,321,575** (Office for National Statistics)
Diabetes prevalence (7.12%): **94,096** (Diabetes UK)
Type 2 diabetes prevalence (90%): **84,686** (Diabetes UK)
Patients intensifying with a GLP-1 receptor agonist (3.8%): **3,218** (NHS Digital).

The annual cost per patient to supply semaglutide is **£954.86.**

Using ePACT data for the year to July 2018, the **average** annual spend per patient on GLP-1 receptor agonists was **£937.45**.

The cost of switching 5% and 10% of patients from their existing GLP-1 receptor agonist to semaglutide is estimated to be:

- To switch 5 % of patients to semaglutide:
  3218 x 937.45 – [(0.05 x 3218 x 954.86) + (0.95 x 3218 x 937.45)]
  = 3,016,714 – (153,733 +2,865,785)
  = 3,016,714 - 3,019,518
  Total additional acquisition cost = £2,804
- To switch 10 % of patients to semaglutide:
  3218 x 937.45 – [(0.1 x 3218 x 954.86) + (0.9 x 3218 x 937.45)]
  = 3,016,714 – (307,465 + 2,714,855)
  = 3,016,714 – 3,022,320
  Total additional acquisition cost = **£5,606**

Please note that these total additional costs are based on the average spend for GLP-1 receptor agonists.

- **Switching to semaglutide from dulaglutide would be cost neutral.**
- **Switching to semaglutide from liraglutide, exenatide daily and exenatide weekly is likely to be cost saving.**
- **Switching to semaglutide from lixisenatide would create a cost pressure.**

Innovation, need, equity:

A range of both weekly and daily GLP-1 receptor agonists are available for the management glycaemic control in type 2 diabetes. Semaglutide has demonstrated statistically significant

reductions in HbA_{1c} and body weight in comparison to exenatide and dulaglutide. It may therefore represent a more cost effective treatment when GLP-1 receptor agonists are being considered.

References

[1] National Institute for Health and Care Excellence, "Type 2 diabetes in adults: management," December 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng28. [Accessed October 2018].

[2] Lancashire Medicines Management Group, "Guideline for antihyperglycaemic therapy in adults with type 2 diabetes," January 2018. [Online]. Available: http://www.lancsmmg.nhs.uk/download/guidelines/Algorithm-for-antihyperglycaemic-therapy-in-adults-with-type-II-V1.3.pdf. [Accessed October 2018].

[3] C Sorli et al, "Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial," *The Lancet Diabetes and Endocrinology,* vol. 5, no. 4, pp. 251-260, 2017.

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Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR
Tel: 01772 644 400 | www.midlandsandlancashirecsu.nhs.uk