



North Staffordshire Clinical Commissioning Group
Stoke-On-Trent Clinical Commissioning Group
University Hospitals of North Midlands NHS Trust
Midlands Partnership NHS Foundation Trust
North Staffordshire Combined Healthcare NHS Trust

New Medicines Committee Briefing

Date of submission

Drug: Ozempic® (semaglutide injection)

is to be reviewed for use within:

Primary care	X
Secondary care	X

Summary

Glucagon-like peptide-1 (GLP-1) receptor agonists have an established role in the management of type 2 diabetes. The GLP-1 receptor agonists included in the current North Staffordshire Joint Formulary are exenatide and liraglutide. The licensed indication for semaglutide includes 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

NICE has recommended GLP 1 mimetics only when

- co-prescribed with metformin and a sulfonylurea, and only if previous triple therapy has been ineffective, not tolerated or contraindicated or
- in combination with insulin if recommended by a specialist care advice and if there is on-going support from a consultant-led multidisciplinary team.

NICE's recommendations is in line with recommendations from the SMC and AWMSG, which recommends that semaglutide is only prescribed as add-on therapy to other oral anti-diabetic products or as an add-on to basal insulin.

Two phase 3 head-to-head studies directly compared semaglutide with comparator GLP-1 mimetics (SUSTAIN 3 and SUSTAIN 7 study) – exenatide (included in NSJF) and dulaglutide (not included in NSJF). The results from both of these showed that semaglutide was associated with significantly better glycaemic control and weight loss compared to exenatide and dulaglutide. The safety and efficacy of semaglutide has also been compared to sitagliptin and insulin glargine, where semaglutide was an add-on therapy to existing oral anti-diabetic medication or insulin. In all these trials, semaglutide has demonstrated superiority in glycaemic control and weight loss. The most common adverse effects reported were gastrointestinal related; although these are reported with other GLP-1 receptor agonists. The SUSTAIN 6 trial demonstrated the cardiovascular risk reduction benefits of semaglutide where the study concluded that patients treated with semaglutide had a 26% lower risk of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke than those in the placebo

group. The risk of retinopathy was greater with semaglutide, which can be attributed to rapid H1BAC reduction

Dr Ananth Nayak proposes that semaglutide is only prescribed as add-on therapy in combination with oral anti-diabetic products or basal insulin as per NICE guidance for GLP-1 mimetics. It is proposed semaglutide would be initiated in secondary care and patients would transfer to primary care after 6 months, if metabolic benefits have been seen. The proposed treatment initiation pathway is as per the treatment initiation and stabilisation pathway for other GLP-1 agonists on the NSJF.

Semaglutide is classified by the MHRA as a black triangle medication, hence is subject to additional monitoring. With the proposed introduction of semaglutide to the NSJF, the UHNM diabetes consultants will also present a review of GLP-1 agonist prescribing to the APC. The suggested new 1st line GLP-1 agonist would be liraglutide 1.2mg daily (Victoza®), followed by semaglutide as second-line and exenatide once weekly (Bydureon®) as third-line.

Formulary application

Consultants submitting application: Dr Ananth Nayak (consultant physician in endocrinology and diabetes).

Clinical Director supporting application: Dr Adrian Walker (consultant physician in endocrinology and diabetes). Dr Walker supports the application as semaglutide appears to provide more effective weight and glucose control compared to other GLP-1 mimetics, with minimal financial impact for the health economy.

Background¹

Glucagon-like peptide-1 (GLP-1) receptor agonists have an established role in the management of type 2 diabetes. Within this class of drugs, differences exist in duration of action, glycaemic control, weight loss, tolerability and administration routines. The long-acting GLP-1 receptor agonists, such as semaglutide are associated with fewer fluctuations in plasma drug concentrations, improved gastrointestinal tolerability and convenient administration routines; resulting in improved adherence.

GLP1 receptor agonists are recommended in NICE guidance (NG28) where

- co-prescribed with metformin and a sulfonylurea, and only if previous triple therapy has been ineffective, not tolerated or contraindicated or
- in combination with insulin if recommended by a specialist care advice and if there is on-going support from a consultant-led multidisciplinary team.

Current formulary status

Semaglutide is not on the current North Staffordshire Joint Formulary.

6.1.2.3 Other antidiabetic drugs			
Acarbose			
Canagliflozin		Restriction: In line with NICE Guidance only For mono, dual & triple therapy and can be continued once initiated until eGFR is <45mL/min/1.73m ²	<input checked="" type="checkbox"/> NICE TA315 <input checked="" type="checkbox"/> NICE TA390
Dapagliflozin		Restriction: In line with NICE Guidance only For mono, dual & triple therapy only and cannot be used if eGFR is <60mL/min/1.73m ²	<input checked="" type="checkbox"/> NICE TA288 <input checked="" type="checkbox"/> NICE TA390 <input checked="" type="checkbox"/> NICE TA418 <input checked="" type="checkbox"/> MTRAC
Empagliflozin		Restriction: In line with NICE Guidance only For mono, dual & triple therapy and can be continued once initiated until eGFR is <45mL/min/1.73m ²	<input checked="" type="checkbox"/> NICE TA336 <input checked="" type="checkbox"/> NICE TA390
Alogliptin		Preferred DPP-4 inhibitor	
Linagliptin			
Sitagliptin			
Pioglitazone		1 st line thiazolidinedione	<input checked="" type="checkbox"/> MTRAC
Repaglinide		Alternative to a sulphonylurea when it is not tolerated or is inappropriate	<input checked="" type="checkbox"/> MTRAC
Exenatide (twice daily) (Byetta®)	2	Restriction: Treatment should be initiated by secondary care endocrinologists and transferred to primary care after six months as long as the patient has had a beneficial metabolic process, i.e. at least a 1% HbA _{1c} reduction <u>AND</u> at least a 3% reduction in weight.	<input checked="" type="checkbox"/> MTRAC
Exenatide (once-weekly) (Bydureon®)	2	Restriction: Only for patients who cannot tolerate twice daily exenatide (Byetta) Restriction: Treatment should be initiated by secondary care endocrinologists and transferred to primary care after six months as long as the patient has had a beneficial metabolic process, i.e. at least a 1% HbA _{1c} reduction <u>AND</u> at least a 3% reduction in weight.	<input checked="" type="checkbox"/> NICE TA248 <input checked="" type="checkbox"/> MTRAC
Liraglutide	2	Restriction: Liraglutide should be used second line to exenatide in patients where exenatide is not tolerated or not effective (i.e. exenatide twice daily (Byetta) was not effective OR exenatide twice daily (Byetta) was not tolerated and exenatide once weekly (Bydureon) was not effective). Patients should receive at least 3 months of exenatide before liraglutide is prescribed. Treatment should be initiated by secondary care endocrinologists and transferred to primary care after 6 months treatment with liraglutide as long as the patient has had a beneficial metabolic process, i.e. at least a 1% HbA _{1c} reduction <u>AND</u> at least a 3% reduction in weight	<input checked="" type="checkbox"/> NICE TA203 <input checked="" type="checkbox"/> MTRAC

The GLP-1 receptor agonists currently included in the NSJF are exenatide and liraglutide.

Summary of GLP-1 agonists included in the formularies of surrounding CCGs, and their associated prescribing categorisations

= included in formulary

GLP-1 agonist	Surrounding area formularies				
	South Staffordshire (including Burton)	Derbyshire *	Wolverhampton	Birmingham and Surrounds	Central and East Cheshire
Albiglutide once weekly (Eperzen®)	DISCONTINUED	<input checked="" type="checkbox"/> Unclassified by Derbyshire JAPC DISCONTINUED	DISCONTINUED	DISCONTINUED	Grey – do not prescribe DISCONTINUED
Dulaglutide once weekly (Trulicity®)	<input checked="" type="checkbox"/> - Amber Preferred weekly GLP-1 agonist (Reviewed February 2017)#.	<input checked="" type="checkbox"/> - Brown – only if weekly preparation is indicated	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Green	<input checked="" type="checkbox"/> ESCA in line with NICE NG28
Exenatide twice daily (Byetta®)	<input checked="" type="checkbox"/> - Amber	<input checked="" type="checkbox"/> - Brown	In line with NG 28	Black – non formulary following review March 2019	<input checked="" type="checkbox"/> ESCA in line with NICE NG 28
Exenatide once weekly	<input checked="" type="checkbox"/> - Amber	<input checked="" type="checkbox"/> - Brown – only if weekly	<input checked="" type="checkbox"/> In line with NG 28. Initiation in	Black – non formulary	<input checked="" type="checkbox"/> ESCA in line with NICE NG28

(Bydureon®)		preparation is indicated	secondary care by diabetologist, then for repeat prescribing in primary care	following review March 2019	
Liraglutide once daily (Victoza®)	<input checked="" type="checkbox"/> - Amber	<input checked="" type="checkbox"/> - Brown= only if weekly preparation is indicated	<input checked="" type="checkbox"/> In line with NG 28. 1.8mg daily not recommended	<input checked="" type="checkbox"/> Green	<input checked="" type="checkbox"/> ESCA. In line with NICE NG28
Lixisenatide once daily (Lyxumia®)	<input checked="" type="checkbox"/> - Red	<input checked="" type="checkbox"/> 1 st line - Green	<input checked="" type="checkbox"/> In line with NG28	Black Non formulary following review March 2019	<input checked="" type="checkbox"/> ESCA. In line with NICE NG28
Semaglutide once weekly (Ozempic®)		<input checked="" type="checkbox"/> - Brown (included February 2019)			<input checked="" type="checkbox"/> ESCA (included March 2019)

#SSJF Diabetes Guidelines published February 2017. Recommendation of dulaglutide as 1st line once weekly GLP-1 agonist made as at the time publication, dulaglutide was the only once weekly preparation licensed for use with insulin. Bydureon® subsequently had license extended to include combination therapy with basal insulin. Semaglutide has subsequently been launched in January 2019, which is once weekly and licensed for use with basal insulin.

*Derbyshire JAPC Guidelines (Management of Type 2 Diabetes in adults) updated July 2018. Green = suitable for primary care prescribing. Brown = not recommended for use except in exceptional circumstances

Therapeutic class and mode of action²

Semaglutide is a glucagon-like peptide-1 analogue (GLP-1) and selectively binds to and activates GLP-1 receptors. These receptors are located in the brain, pancreas, heart, immune system and kidneys. Activation of these receptors in the pancreas, allows regulation of glucose through insulin secretion and lowering glucagon secretion. It also results in delayed gastric emptying during the early postprandial phase. Additional effects include a reduction in body weight, fat mass, plasma lipids, and systolic blood pressure. Semaglutide binds to albumin resulting in reduced renal clearance and metabolic degradation; allowing once weekly administration.

Licensed indications²

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

In comparison to other GLP-1 agonists currently on the NSJF, semaglutide's indication matches that for Victoza® (liraglutide 6mg/ml), which is the proposed 1st line GLP-1 agonist on the NSJF.

The proposed 3rd line GLP-1 agonist, Bydureon® (2mg/0.65ml once weekly), is licensed in adults with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control.

Byetta® (the proposed 4th line GLP-1 agonist) is indicated for treatment of type 2 diabetes mellitus in combination with other oral glucose-lowering medicinal products (metformin, sulphonylureas, thiazolidinediones, metformin and a sulphonylurea, metformin and a thiazolidinedione) or as

adjunctive therapy to basal therapy with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these medicinal products.

Immediate-release exenatide (Byetta) therapy should be initiated at 5 mcg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 mcg BID to further improve glycaemic control. Doses higher than 10 mcg BID are not recommended.

Dosage and administration²

The recommended starting dose for semaglutide injection is 0.25 mg once weekly. After 4 weeks, dose should be increased to 0.5 mg once weekly and then further increased after 4 weeks to 1mg once weekly.

Semaglutide is for subcutaneous administration into the abdomen, thigh or upper arm. It can be administered with or without food and taken at any time of the day.

When added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged. Additionally, if semaglutide is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia.

Blood glucose monitoring is not required for dose adjustments. If initiated in combination with a sulfonylurea or an insulin, blood glucose monitoring may be necessary to adjust the dose of the sulfonylurea or the insulin.

If a dose is missed, semaglutide should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day.

Safety and adverse effects^{1,2}

Warnings and precautions

The main adverse effect associated with GLP-1 receptor agonist treatment such as semaglutide is gastrointestinal related (i.e. nausea, vomiting and diarrhoea). These are usually mild to moderate in severity and diminish over time. This is as per other GLP-1 receptor agonists.

Precautions associated with GLP-1 agonists included in the NSJF (exenatide or liraglutide) vs semaglutide		
Exenatide (Byetta(r) or Bydureon®)	Liraglutide (Victoza®)	Semaglutide (Ozempic®)
Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min). The clinical experience in patients with moderate renal impairment is very limited	There is no therapeutic experience in patients with end-stage renal disease, and Victoza® is therefore not recommended for use in these patients	Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease
Caution should be exercised in patients with a history of	Acute pancreatitis has been observed with the use of GLP-1	Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Caution

<p>pancreatitis, as GLP-1 agonists have been associated with a risk of developing acute pancreatitis</p> <p>Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of exenatide is not recommended in patients with severe gastrointestinal disease</p>	<p>receptor agonists, therefore caution in patients with a history of pancreatitis</p> <p>Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with liraglutide. 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.</p> <p>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</p> <p>Thyroid adverse events, such as goitre, have been reported in clinical trials and in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in these patients.</p>	<p>should be exercised in patients with a history of pancreatitis.</p> <p>Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function (see section 4.8).</p> <p>In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded</p>
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Contraindications

Semaglutide is contraindicated in patients with hypersensitivity to the active substance or to any of its excipients. Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin.

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

See below for comparison of contraindications associated with GLP-1 agonists included in the NSJF vs semaglutide

Contraindications for GLP-1 agonists included in the NSJF (exenatide and liraglutide) vs semaglutide		
Exenatide (Byetta® or Bydureon®)	Liraglutide (Victoza®)	Semaglutide (Ozempic®)
<p>Exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.</p> <p>Exenatide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin</p>	<p>Do not use in patients with hypersensitivity to the active ingredient or excipients</p> <p>Liraglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.</p> <p>Liraglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).</p> <p>There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV, and liraglutide is therefore not recommended for use in these patients.</p>	<p>Do not use in patients with hypersensitivity to the active ingredient or excipients</p> <p>Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin.</p> <p>There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.</p>

Drug Interactions²

Similar to existing GLP-1 receptor agonists, semaglutide does not affect the pharmacodynamic properties of warfarin; although its manufacturers recommend frequent INR monitoring during treatment initiation. Additionally, existing GLP-1 receptor agonists plus semaglutide delay gastric emptying and should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption.

Presentation²

Semaglutide is available as a 0.25mg, 0.5mg and 1mg solution for injection in pre-filled pen.

The prefilled pen consists of a 1.5 ml or 3 ml glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Patent Status²

Date of first authorisation/renewal of the authorisation: 08 February 2018

Date of revision of the text: 10/2018

Guidance and Evidence Summary**NICE Guidance^{3,4}****Y**

According to NICE guidance on the management of type 2 diabetes (NG 28, published December 2015. Last updated May 2017), when triple therapy with metformin and two other oral anti-diabetic drugs has been ineffective or is contraindicated, a GLP-1 mimetic is recommended. NICE recommend the use of a GLP-1 mimetic in combination with metformin and a sulfonylurea. This triple therapy is recommended in patients who:

- have a BMI of 35 kg/m² or higher and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

GLP-1 mimetic therapy can also be offered in combination with insulin; although this should follow specialist care advice. NICE also recommend that GLP-1 mimetic therapy should only continue if the patient has had a beneficial metabolic response (a reduction of at least 11 mmol/mol (1.0%) in HbA_{1c} and a weight loss of at least 3% of initial body weight in 6 months).

Alongside its ability to lower glucose, GLP-1 receptor agonists have the advantage of promoting weight loss; consequently restrictions are needed against its widespread use as outlined by NICE. Additionally, GLP-1 receptor agonists are more expensive than oral anti-diabetic drugs and basal insulin, which also influences the recommendations outlined by NICE. Although treatment may be considered more cost effective in patients with a high BMI, due to the greater anticipated weight loss.

NICE is planning to publish a Technology Appraisal Guidance for semaglutide, but this is currently undergoing consultation on suggested remit, draft scope and provisional matrix of consultees and commentators

Scottish Medicines Consortium (SMC)⁵**Y**

Semaglutide is accepted for restricted use within NHS Scotland in addition to other oral anti-diabetic medicines, or as an add-on to basal insulin, as an alternative glucagon-like peptide-1 receptor agonist option. SMC cannot recommend the use of semaglutide as monotherapy when metformin is considered inappropriate due to intolerance or contraindications as the company's submission related only to its use in addition to other medicinal products for the treatment of diabetes.

All Wales Medicines Strategy Group (AWMSG)⁶**Y**

Semaglutide is recommended as an option for restricted use within NHS Wales for the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an add-on therapy to oral anti-diabetic medicines or basal insulin. Semaglutide is not recommended for use within NHS Wales as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.

Similar to the SMC, this submission focused on the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an add-on therapy to oral anti-diabetic medicines or basal insulin.

Regional Drug and Therapeutic Centre (RDTC) ⁷	Y
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Semaglutide is a GLP1 receptor agonist (GLP1RA) indicated as an adjunct to diet and exercise for the treatment of adults with insufficiently controlled type 2 diabetes mellitus. A large phase III clinical trial programme found that semaglutide was generally associated with greater reductions in HbA1c, body weight and fasting plasma glucose than comparators, which included placebo, sitagliptin, exenatide, dulaglutide and insulin glargine. A cardiovascular outcomes trial found that semaglutide reduced the compound risk of stroke, myocardial infarction and cardiovascular death compared to placebo in people with a history of cardiovascular disease. The safety profile of semaglutide was in line with the other marketed GLP1RAs, although there may be an increased risk of diabetic retinopathy complications in people with existing retinopathy. Semaglutide has a similar price to the other marketed GLP1 mimetics

Midlands Therapeutics Review and Advisory Committee (MTRAC)	N
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Efficacy ⁸⁻¹⁴

The safety and efficacy of semaglutide has been demonstrated in several clinical trials including:

- **SUSTAIN 1** - Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes.
- **SUSTAIN 2** - Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes.
- **SUSTAIN 3** - Efficacy and Safety of Semaglutide Once-weekly Versus Exenatide ER 2.0 mg Once-weekly as add-on to 1-2 Oral Antidiabetic Drugs (OADs) in Subjects with Type 2 Diabetes.
- **SUSTAIN 4** - Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes.
- **SUSTAIN 7** – Efficacy and Safety of Semaglutide Versus Dulaglutide as add-on to Metformin in Subjects with Type 2 Diabetes.

In these trials, the primary and secondary endpoints were a change in mean HbA1c and body weight from baseline. In all these trials, semaglutide demonstrated superiority in glycaemic control and weight loss. These trials illustrated that the most common adverse effect experienced with semaglutide was gastrointestinal related. Additionally, the impact of switching from one GLP-1 receptor agonist to semaglutide was investigated by exposure-response models. The results of this model state that switching from liraglutide, dulaglutide or exenatide to semaglutide results in further reductions in HbA1C and body weight.

The cardiovascular safety of semaglutide was demonstrated in SUTAIN 6. This was a randomized, double-blind, placebo-controlled, parallel group trial at 230 sites in 20 countries. 3297 patients with type 2 diabetes were randomly assigned to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. At baseline, 2735 patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group. Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and 3.9% of those receiving placebo. Nonfatal stroke occurred in 1.6% of the patients receiving semaglutide and 2.7% in the placebo group. Rates of new or worsening nephropathy were lower in the semaglutide

group, but rates of retinopathy complications were significantly higher with semaglutide. Similar to previous trials, SUSTAIN 6 also demonstrated that glycaemic control and body weight decreased greater with semaglutide 0.5mg or 1mg compared to placebo. Gastrointestinal adverse effects (e.g. diarrhoea, vomiting and nausea) were more common in the semaglutide group; although these were mild-moderate in severity and occurred during the first 30 weeks. The authors of this study concluded that the patients treated with semaglutide had a 26% lower risk of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke than those in the placebo group.

Cost Analysis

Medication	Dose when used as adjunctive therapy (as per NG 28)	Cost of 12 months (52 weeks) supply per patient excl. VAT (Primary care price)	Cost of 12 months supply per patient incl. VAT (Secondary care price)	Included in NSJF?
Dulaglutide	1.5mg once weekly	£952.25	£1142.70	
Exenatide daily (Byetta®)	5mcg bd for at least one month, then increase if required to 10mcg bd .	£982.68	£1179.22	<input checked="" type="checkbox"/>
Exenatide 2mg (Bydureon®)	2mg once weekly	£880.32	£1056.38	<input checked="" type="checkbox"/>
Liraglutide 18mg/3ml	1.2mg once daily	£941.76	£1130.11	<input checked="" type="checkbox"/>
Liraglutide 18mg/3ml	1.8mg once daily (maximum dose) NB in practice most patients maintained on 1.2mg once daily	£1,412.64	£1695.17	<input checked="" type="checkbox"/>
Lixisenatide	10mcg daily for 14/7, then increase to 20mcg once daily	£697.86	£837.48	
Semaglutide initiation and maintenance	Treatment initiation with Semaglutide starting from 0.25mg once weekly for 4 weeks, then increased to 0.5mg once weekly for 4 weeks and then increased to 1mg once weekly (maintenance dose)	£879	£1054.80	

It is proposed that semaglutide would be prescribed instead of exenatide once weekly (which is the current 2nd line GLP-1 mimetic).

Since semaglutide is similarly priced to liraglutide and exenatide once weekly, it is predicted that adding semaglutide to the NSJF will have minimal financial impact for the health economy.

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