North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Ozempic® (semaglutide solution for injection)

Verdict:	
Formulary inclusion:	To be included in the North Staffordshire Joint Formulary
Formulary category:	Amber
Restrictions:	- To be initiated by secondary care diabetes team. - Prescribing can be transferred to primary care after 6 months if patients achieves at least a 1% HbA1C reduction and at least a 3% reduction in weight
Reason for inclusion:	The Area Prescribing Committee was satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy.
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians→ Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Review summary:

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: 26/06/2019

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Formulary application:

A formulary application for Ozempic® (semaglutide solution for injection) was presented to the New Medicines Committee on 03/04/2019 .Dr Ananth Nayak (consultant physician in endocrinology and diabetes) submitted and presented the application. The application is supported by Dr Adrian Walker (consultant physician in endocrinology and diabetes).

Drs Nayak and Walker envisage semaglutide will be

- co-prescribed with metformin and a sulfonylurea, and only if previous triple therapy has been ineffective, not tolerated or contrainidicated or
- in combination with insulin

This is as per NICE recommendations for prescribing GLP-1 agonists (NG28) and is line with prescribing of current GLP-1 agonists on the NSJF. These prescribing restrictions are also as per the SMC's and AWMSG's recommendations.

The UHNM endocrinology team supports the proposed addition of semaglutide to the NSJF as

- semaglutide appears to provide more effective weight and glucose control compared to other GLP-1 agonists available on the NSJF
- semaglutide is a once weekly formulation
- Semaglutide is less expensive than liragultide 1.2mg daily (Victoza®) and is similarly priced to exenatide once weekly (Bydureon®) which are the current 2nd and 1st line GLP-1 agonists respectively. Introduction of semaglutide injection to the formulary is thus predicted to have minimal financial impact for the Staffordshire Health Economy.
    - Prescribing of GLP-1 agonists will also be reviewed in tandem with the proposal to add Ozempic® to the NSJF

Licensed indications:

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 OR
- in addition to other medicinal products for the treatment of diabetes

Dosing:

The recommended starting dose 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.

Related guidance:

NICE:

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/m2and 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 HbA1c 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 ("Semaglutide for treating type 2 diabetes"), but this is currently undergoing consultation on suggested remit, draft scope and provisional matrix of consultees and commentators

SMC:

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.

RDTC:

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

MTRAC:
MTRAC have not reviewed semaglutide

Background information:

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.

Efficacy:

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.

Safety:

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 pancreatitis, as GLP-1 agonists have been associated with a risk of developing acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 receptor agonists, therefore caution in patients with a history of pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Caution should be exercised in patients with a history of pancreatitis.
Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse	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	Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal

reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of exenatide is not recommended in patients with severe gastrointestinal disease	potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. 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	function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function (see section 4.8).
	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.	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

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.

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	Liraglutide (Victoza®)	Semaglutide (Ozempic®)

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Bydureon®)		
Exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Exenatide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin	Do not use in patients with hypersensitivity to the active ingredient or excipients Liraglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. 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). 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.	Do not use in patients with hypersensitivity to the active ingredient or 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.

Place in therapy:
The diabetes consultants propose a review of GLP-1 agonist prescribing with the introduction of semaglutide. The suggested new pathway is

1. Victoza® 1.2mg daily
2. Ozempic® 1mg weekly maintenance
3. Bydureon 2mg once weekly
4. Byetta 10mcg bd

Cost:

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	5mcg bd for at least one month, then increase if	£982.68	£1179.22	☑

(Byetta®)	required to 10mcg bd .			
Exenatide 2mg (Bydureon®)	2mg once weekly	£880.32	£1056.38	☑
Liraglutide 18mg/3ml	1.2mg once daily	£941.76	£1130.11	☑
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	☑
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	

References:

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