Mid and South Essex Health and Care Partnership

NHS

MID AND SOUTH ESSEX MEDICINES OPTIMISATION COMMITTEE (MSEMOC)

DULAGLUTIDE (TRULICITY®) FOR TYPE 2 DIABETES MELLITUS

YELLOW - RECOMMENDED FOR RESTRICTED USE - for initiation by SPECIALISTS with relevant clinical experience in managing diabetes and for continuation in primary care

Name: generic (trade)	What it is	Indication	Decision status	NICE/SMC guidance
Dulaglutide (Trulicity®)	Glucagon-like peptide-1 (GLP-1) receptor agonist	Type 2 diabetes mellitus (T2DM)	Final	NICE - none SMC - approved for restricted use

MSEMOC recommendation:

Dulaglutide (Trulicity®) is recommended for restricted use as a GLP-1 receptor agonist when a GLP-1 receptor agonist is indicated in accordance with the type 2 diabetes mellitus – anti-hyperglycaemic treatment pathway. Dulaglutide must be initiated by SPECIALISTS with relevant clinical experience and training in managing diabetes and can be continued in primary care.

Monotherapy regime:

- **ONLY** in patients when control of blood glucose remains or becomes inadequate **(HbA1c ≥53 mmol/mol [7%] or greater than individualised target)**:
  - with a high cardiovascular risk **and**
  - if metformin is contraindicated/not tolerated **and**
  - in whom a sodium-glucose co-transporter 2 inhibitor (SGLT2i) is contraindicated

  And the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

Dual therapy regime:

- **With metformin or a sulphonylurea or pioglitazone or SGLT2i** in patients when control of blood glucose remains or becomes inadequate **(HbA1c ≥53 mmol/mol [7%] or greater than individualised target)**

  And the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

Triple therapy regime:

- **With metformin and a sulphonylurea, or metformin and a SGLT2i, or metformin and pioglitazone, or pioglitazone and a sulphonylurea** in patients when control of blood glucose remains or becomes inadequate **(HbA1c ≥53 mmol/mol [7%] or greater than individualised target) And** the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

The majority of patients will be stabilised on a 1.5mg once weekly dose of dulaglutide at which the benefit risk ratio is most favourable. Refer to diabetes specialist for consideration of higher strength dulaglutide (3mg once weekly and 4.5mg once weekly) for patients that fail to achieve target on 1.5mg once weekly dose, or for consideration of alternative treatment options as appropriate.

Background information

- Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist, that exhibits GLP-1–mediated effects, including glucose-dependent potentiation of insulin secretion, decrease in glucagon secretion, delay of gastric emptying, and decrease in appetite. Due to its prolonged half-life, it is suitable for once-weekly subcutaneous administration.
- Dulaglutide is licensed in type 2 diabetes mellitus and 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
- The recommended dosage as monotherapy is 0.75 mg once weekly and as add-on therapy is 1.5 mg once weekly. For potentially vulnerable populations, such as patients ≥ 75 years, 0.75 mg once weekly can be considered as a starting dose. For additional glycaemic control, the 1.5 mg dose may be increased after at least four weeks to 3 mg once weekly. The 3 mg dose may be increased after at least four weeks to 4.5 mg once weekly. The maximum dose is 4.5 mg once weekly.
- Dulaglutide is to be injected subcutaneously only in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals.
- Dulaglutide is available as single-use pens. It should be stored in a refrigerator (2-8 °C) but may be stored unrefrigerated for up to 14 days at up to 30°C.

PROPOSED ASSESSMENT AGAINST THE ETHICAL FRAMEWORK
– to be agreed by committee

Evidence of Clinical Effectiveness:

Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11, Frias et al, 2021)

- *Design*: Patients were randomly assigned to once-weekly dulaglutide 1.5 mg, 3.0 mg, or 4.5 mg for 52 weeks. The primary objective was determining superiority of dulaglutide 3.0 mg and/or 4.5 mg over 1.5 mg in HbA1c reduction at 36 weeks. Secondary superiority objectives included change in body weight. Two estimands addressed efficacy objectives: treatment regimen (regardless of treatment discontinuation or rescue medication) and efficacy (on treatment without rescue medication) in all randomly assigned patients.
- *Patients*: Eligible adults (aged ≥18 years) had type 2 diabetes for ≥6 months, with HbA1c ≥7.5% (58 mmol/mol) and ≤11.0% (97 mmol/mol) at screening; BMI ≥25 kg/m2; were insulin and GLP-1 RA naive; and were taking commercially available metformin ≥1,500 mg/day for ≥3 months. A minimum BMI threshold was used to minimize concerns that higher drug exposures, as seen in previous studies with lower-weight patients, might predispose patients with lower BMI to GI tolerability limitations during dose escalation. Patients with type 1 diabetes; those using any other glucose-lowering medications (other than metformin) within 3 months before randomization; serum calcitonin level ≥20 ng/L; a history of pancreatitis, ketoacidosis, or hyperosmolar state/coma; recent CV event; or active cancer were excluded.
- *Intervention and comparator*: This randomized, double-blind, parallel arm study included three periods: a 2-week lead-in period, followed by a 52-week treatment period (with primary efficacy end point at 36 weeks) and a 4-week safety follow-up period. Patients were randomly assigned 1:1:1 to dulaglutide 1.5 mg, 3.0 mg, or 4.5 mg, administered once weekly via subcutaneous injection with a single-dose pen. Randomization was stratified by HbA1c (<8.5% [69 mmol/mol], and ≥8.5% [69 mmol/mol]). Consistent with current labelling recommendations in the U.S., treatment was initiated with once-weekly dulaglutide 0.75 mg. After four weeks, the dose was escalated every 4 weeks to the randomized dose of 1.5 mg, 3.0 mg, or 4.5 mg.
- *Outcomes*: The primary efficacy measure was the change inHbA1c from baseline to 36 weeks. Secondary efficacy measures (all assessed at 36 weeks and controlled for type I error) were the proportion of patients achieving HbA1c <7.0%; change from baseline in fasting serum glucose (FSG) level, determined by the central laboratory; and change from baseline in body weight. All other efficacy measures were exploratory and included comparison of dulaglutide 3.0 mg and 4.5 mg to the 1.5-mg dose at 52 weeks on the primary and secondary efficacy measures, as well as assessment at 36 and 52 weeks of the proportion of patients achieving the HbA1c target of ≤6.5% (48 mmol/mol), six-point self-monitored plasma glucose profile, fasting glucagon level, and measures of insulin resistance and b-cell function.
- *Results:* Mean baseline HbA1c and BMI in randomly assigned patients was 8.6% (70 mmol/mol) and 34.2 kg/m2, respectively. At 36 weeks, dulaglutide 4.5 mg provided superior HbA1c reductions compared with 1.5 mg (treatment-regimen estimand: 21.77 vs. 21.54% [219.4 vs. 216.8 mmol/mol], estimated treatment difference [ETD] 20.24% (22.6 mmol/mol). Dulaglutide 3.0 mg was superior to 1.5 mg for reducing HbA1c. Dulaglutide 4.5 mg was superior to 1.5 mg for weight loss at 36 weeks for both estimands. Common adverse events through 36 weeks included nausea (1.5 mg, 13.4%; 3 mg, 15.6%; 4.5 mg, 16.4%) and vomiting (1.5 mg, 5.6%; 3 mg, 8.3%; 4.5 mg, 9.3%).
  Overall, the AWARD-11 trial demonstrated glycaemic and weight benefits for patients using 3- and 4.5-mg doses of dulaglutide once weekly, without meaningful changes to the safety profile already familiar to clinicians and patients using dulaglutide.

RCT evaluating the safety and efficacy of dulaglutide in combination with metformin and pioglitazone compared with exenatide or placebo (AWARD 1, Wysham et al. 2014)

- *Objective:* To compare the efficacy and safety of dulaglutide, a once-weekly GLP-1 receptor agonist, with placebo and exenatide in type 2 diabetic patients. The primary objective was to determine superiority of dulaglutide 1.5 mg versus placebo in HbA1c change at 26 weeks.
- *Design:* US and South American, multicentre, 52-week, randomised, double-blind to placebo and parallel group study with active control (open-label). Randomisation was stratified by country. Allocation was concealed.
- *Population*: 978 adults (mean age 56 years ±10 years; 58% male) with a long duration of type 2 diabetes (mean 9 years) and several co-morbidities, were randomised to treatment. Two people did not receive any treatment and so the intention-to-treat population was 976. People were eligible for inclusion if they had a body mass index (BMI) between 23 and 45 kg/m2 (mean BMI 33 kg/m2) and HbA1c between 53 and 97 mmol/mol (7% and 11%) on oral monotherapy for blood glucose control or between 53 and 86 mmol/mol (7% and 10%) on a combination of oral therapies for blood glucose control. People were excluded if they had received treatment with GLP-1 receptor agonists within the previous 3 months or were on long-term insulin therapy. Demographic and baseline characteristics were balanced across all treatment arms.
- *Intervention and comparator*: Following a 12-week run-in period where people were up titrated to maximally tolerated doses of metformin (1,500 to 3,000 mg per day) and pioglitazone (30 to 45 mg per day), people were randomised to one of four treatment arms of subcutaneous injections as follows:
  - dulaglutide 0.75 mg once weekly
  - dulaglutide 1.5 mg once weekly
  - exenatide 5 microgram twice daily for four weeks, then 10 microgram twice daily (for the remainder of the study)
  - placebo once weekly

  People in the dulaglutide or placebo arms were blinded to treatment allocation (as were investigators). After 26 weeks, people on placebo were switched in a blinded fashion to

dulaglutide 0.75 mg or 1.5 mg. Add-on rescue therapy was permitted for people in any treatment arm who met predefined criteria for persistent, severe hyperglycaemia.
Participants who received rescue therapy were included in the analysis population, but only measurements obtained prior to the beginning of rescue therapy were included in specified analyses. At randomisation, 86% of people were receiving more than 2500 mg of metformin per day and 45 mg pioglitazone per day and the mean doses were similar across both treatment arms.

- *Outcomes:* The study was designed with 90% power to show superiority of dulaglutide compared with placebo and 93% power for non-inferiority compared with exenatide (with a
non-inferiority margin of 0.4%). The primary outcome measure was the change in HbA1c from baseline to week 26 in the intention-to-treat population (all randomised patients who received at least 1 dose of study treatment). This was evaluated using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) method to handle missing data. Secondary outcome measures included effects on body weight; proportion of participants achieving a target HbA1c less than 53 mmol/mol (7%); and change in HbA1c from baseline to week 52 between dulaglutide and exenatide in the intention-to-treat population.
The 52-week data for those participants switched from placebo at 26 weeks are included in separate analyses and are not discussed in this evidence summary. Long-term, comparator-controlled safety and efficacy data were collected through to the final time points. Safety assessments included the occurrence of adverse events and hypoglycaemic episodes.
- *Results:* Dulaglutide 1.5 mg and 0.75 mg once weekly (added to metformin and pioglitazone) were superior to placebo and exenatide twice daily for change in HbA1c from baseline (average 65.0 mmol/mol [8.1%], p<0.001 for all comparisons). At 26 weeks, the reduction in HbA1c was 16.5 mmol/mol (1.51%) with dulaglutide 1.5 mg; 14.2 mmol/mol (1.30%) with dulaglutide 0.75 mg; 10.8 mmol/mol (0.99%) with exenatide; and 5.0 mmol/mol (0.46%) with placebo.

RCT evaluating the safety and efficacy of dulaglutide in combination with metformin compared with sitagliptin or placebo (AWARD 5, Nauck et al. 2014)

- *Objective:* To compare the efficacy and safety of two doses of once-weekly dulaglutide, a glucagon-like peptide 1 receptor agonist, to sitagliptin in uncontrolled, metformin-treated patients with type 2 diabetes. The primary objective was to compare (for noninferiority and then superiority) dulaglutide 1.5 mg versus sitagliptin in change from baseline in glycosylated hemoglobin A1c (HbA1c) at 52 weeks.
- *Design:* Worldwide, multicentre, 104-week, randomised, double-blind and parallel group study with active control. Allocation was concealed.
- *Population:* 1,098 adults (mean age 54 years; 48% male) with a long duration of type 2 diabetes (mean 7 years) were randomised to treatment. People were eligible for inclusion if they had a body mass index (BMI) between 25 and 45 kg/m2 (mean BMI 31 kg/m2) and HbA1c of more than 64 mmol/mol (8%) and less than or equal to 80 mmol/mol (9.5%) on diet and exercise alone or between 53 and 80 mmol/mol (7% and 9.5%) on oral treatment for blood glucose control. Around 94% of the group were taking oral treatment for blood glucose control at baseline. People were excluded if they had received treatment with GLP-1 receptor agonists within the previous 6 months or were on long-term insulin therapy. Demographic and baseline characteristics were balanced across all treatment arms.
- *Intervention and comparator:* Following an 11-week run-in period to ensure participants were titrated to a stable dose of metformin (minimum dose1500 mg per day) and had washed out all other oral treatments for blood glucose control, people were randomised to 1 of 2 sequential randomisation schemes: adaptive randomisation during a dose finding period (n=230, to identify a safe and efficacious low and high dose of dulaglutide), followed by fixed randomisation after dose selection (Geiger et al. 2012). After dulaglutide 0.75 mg and 1.5 mg were selected as the identified doses for the next phase of the study, participants from non-selected dose arms discontinued treatment. Additional participants were then randomised to one of the four following treatment arms (in a 2:2:2:1 ratio):
  - dulaglutide 0.75 mg once weekly (subcutaneous injection)
  - dulaglutide 1.5 mg once weekly (subcutaneous injection)
  - sitagliptin 100 mg once daily (tablet)
  - placebo (once daily tablet and once weekly subcutaneous injection).

  After 26 weeks, people on placebo were switched in a blinded fashion to sitagliptin 100 mg once daily. Data from people in the placebo arm were excluded from any analysis after 26 weeks. People in any treatment arm who met predefined criteria for persistent or worsening hyperglycaemia were discontinued from the study.
- *Outcomes:* The study was designed to demonstrate the non-inferiority then superiority of dulaglutide 1.5 mg compared with sitagliptin (with a non-inferiority margin of 0.25%). The primary outcome measure was change in HbA1c from baseline to week 52 between dulaglutide at both doses and sitagliptin in the intention-to-treat population (all randomised patients who received at least 1 dose of study treatment, had a baseline assessment and at least 1 post-baseline assessment of HbA1c). The data from the placebo arm were excluded after 26 weeks. Data were evaluated using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) method to handle missing data. Secondary outcome measures included change in HbA1c from baseline to other time points, between dulaglutide and the comparators in the intention-to-treat population; effects on body weight; and proportion of participants achieving target HbA1c less than 53 mmol/mol (7%). Long-term, comparator-controlled safety and efficacy data were collected through to the final time points. Safety assessments included the occurrence of adverse events and hypoglycaemic episodes.
- *Results:* Dulaglutide 1.5 mg and 0.75 mg once weekly were superior to sitagliptin 100 mg once daily (all in addition to background metformin 1500 mg or more daily) for change in HbA1c from baseline (average 65.0 mmol/mol [8.1%], p<0.001 for both comparisons). At 52 weeks, the reduction in HbA1c was 12.0 mmol/mol (1.10%) with dulaglutide 1.5 mg; 9.5 mmol/mol (0.87%) with dulaglutide 0.75 mg; and 4.3 mmol/mol (0.39%) with sitagliptin.

RCT evaluating the safety and efficacy of dulaglutide 1.5 mg in combination with metformin compared with liraglutide 1.8 mg (AWARD 6, Dungan et al. 2014)

- *Objective:* Comparing the safety and efficacy of once-weekly dulaglutide with that of once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes.
- *Design:* Multicentre (nine countries in total from Europe, Mexico and USA), 26-week, randomised, open-label, parallel group study with active control. Randomisation was stratified by country and HbA1c. Allocation was concealed. Population: 599 adults (mean age 57 years; 48% male) with a long duration of type 2 diabetes (mean seven years) were randomised to treatment. People were eligible for inclusion if they had a BMI of 45 kg/m2 or less (mean BMI 33.6 kg/m2) and HbA1c of more than 53 mmol/mol (7%) and less than or equal to 86 mmol/mol (10%)) and were receiving a stable dose of metformin (1,500 mg or more per day) for three months or longer. People were excluded if they were taking other therapies to control blood glucose, had a history of pancreatitis or recent cardiovascular event. Other exclusions, including abnormal biochemical markers also applied. Demographic and baseline characteristics were balanced across all treatment arms.
  Intervention and comparator: Following a two-week screening period, eligible people were randomised in a 1:1 ratio to either:
  - dulaglutide 1.5 mg once weekly (subcutaneous injection) or
  - liraglutide 1.8 mg once daily (subcutaneous injection, up-titrated from starting dose of 0.6 mg once daily over three weeks).

The study consisted of 26 weeks treatment and four weeks safety follow up. Add-on rescue therapy was permitted for people in any treatment arm who met predefined criteria for persistent, severe hyperglycaemia but efficacy and hypoglycaemia measures only included data obtained before rescue drugs were given.

- *Outcomes:* The study was designed to demonstrate non-inferiority of dulaglutide 1.5 mg compared with liraglutide 1.8 mg (with a non-inferiority margin of 0.4%).The primary outcome measure was change in HbA1c from baseline to week 26 between dulaglutide and liraglutide in the intention-to-treat population (all randomised patients who received at least 1 dose of study treatment). Data were evaluated using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) method to handle missing data. Secondary outcome measures included effects on body weight and proportion of participants achieving target HbA1c less than 53 mmol/mol (7%). Safety assessments included the occurrence of adverse events and hypoglycaemic episodes.
- *Results:* Dulaglutide 1.5 mg once weekly was non-inferior to liraglutide 1.8 mg once daily (both in addition to pre-existing stable metformin 1500 mg or more daily) for change in HbA1c from baseline (average 65.0 mmol/mol [8.1%]). At 26 weeks, the reduction in HbA1c was 16 mmol/mol (1.42%) with dulaglutide compared with 15 mmol/mol (1.36%) with liraglutide (p<0.0001 for non-inferiority).

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWARD)[18]

- Background: Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A1c (HbA1c) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.
- Methods: This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population.
- Findings: Between Aug 18, 2011, and Aug 14, 2013, 9901 participants (mean age 66·2 years [SD 6·5], median HbA1c 7·2% [IQR 6·6–8·1], 4589 [46·3%] women) were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). During a median follow-up of 5·4 years (IQR 5·1–5·9), the primary composite outcome occurred in 594 (12·0%) participants at an incidence rate of 2·4 per 100 person-years in the dulaglutide group and in 663 (13·4%) participants at an incidence rate of 2·7 per 100 person-years in the placebo group (hazard ratio [HR] 0·88, 95% CI 0·79–0·99; p=0·026). All-cause mortality did not differ between groups (536 [10·8%] in the dulaglutide group vs 592 [12·0%] in the placebo group; HR 0·90, 95% CI 0·80–1·01; p=0·067). 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001).
- Interpretation: Dulaglutide could be considered for the management of glycaemic control in middle-aged and older people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

Safety
The most frequently reported adverse reactions in clinical trials were gastrointestinal, including nausea, vomiting and diarrhoea.

Metabolism and nutrition disorders
Hypoglycaemia (when used in combination with insulin, glimepiride, metformin† or metformin plus glimepiride were reported as very common. Hypoglycaemia (when used as monotherapy or in combination with metformin plus pioglitazone) were reported as common.

Gastrointestinal disorders
Nausea, diarrhoea, vomiting, abdominal pain were reported as very common. They were typically mild or moderate in severity and were reported to peak during the first two weeks of treatment and rapidly decline over the next 4 weeks, after which the rate remained relatively constant. Decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastroesophageal reflux disease, eructation were reported as common**.**

General disorders and administration site conditions
Fatigue was reported as common.

Investigations

- Sinus tachycardia, first degree atrioventricular block (AVB) were reported as common.
- The use of Trulicity® does not require blood glucose self-monitoring. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity® therapy is started and insulin is reduced.

Overdose
Effects of overdose with dulaglutide in clinical studies have included gastrointestinal disorders and hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Cost of treatment and Cost Effectiveness:

- All strengths of dulaglutide pre-filled syringes are the same price (£73.25 for a pack of four pre-filled injections) and dose per volume is the same so dose titration would not increase costs.
- There are no additional cost pressures expected with the introduction of the higher strengths. There is potential for cost savings in those patients needing the higher doses using the higher strength pens (3mg and 4.5mg) as the lower strengths require larger volumes to be administered for dose optimisation.

Drug	Usual dose	Drug Tariff/DM+D price (May 2021)
Dulaglutide (Trulicity®) 0.75mg/0.5ml solution for injection pre-filled pens (4 pack)	Weekly	£73.25
Dulaglutide (Trulicity®) 1.5mg/0.5ml solution for injection pre-filled pens (4 pack)	Weekly	£73.25
Dulaglutide (Trulicity®) 3mg/0.5ml solution for injection pre-filled pens (4 pack)	Weekly	£73.25
Dulaglutide (Trulicity®) 4.5mg/0.5ml solution for injection pre-filled pens (4 pack)	Weekly	£73.25

Price comparison with other weekly GLP-1 receptor agonists on formularies within Mid and South Essex:

	Dulaglutide (Trulicity®) 0.75mg, 1.5 mg, 3mg, 4.5mg	**Semaglutide (Ozempic®) 0.25mg, 0.5mg, 1mg**	**Exenatide (Bydureon®) 2mg**
Injection frequency	Once weekly	Once weekly	Once weekly
Injection method	Prefilled pen, needle included	Prefilled pen, needle included	Prefilled pen, needle included
Pack price	£73.25 for 4 pens* (1 pen single use only)	£73.25 for 1 pen* delivering 4 doses	£73.36 for 4 pens* (1 pen single use only)

*All strengths are same price. Prices obtained from May 2021 Drug Tariff.

The needs of the population:

- The needs of the population appear low as there are other alternative, weekly GLP-1 receptor agonists available, however, although exenatide is available in a weekly dose formulation, this does not have beneficial cardiovascular outcome data from large RCTs for at risk cohorts. There is a group of patients already prescribed dulaglutide who may benefit from further optimal glycaemic control/possible further weight loss with the same drug. Dose optimisation with the same drug may prevent a switch to an alternative choice or initiation of insulin. Dose optimisation using lower strengths (0.75mg and 1.5mg) would result in a cost pressure as increased amounts of the lower strengths would need to be prescribed; the use of the higher strengths (3mg and 4.5mg) reduces that cost pressure as they cost the same as the lower strengths and an increase in prescribing quantity is not required.
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The needs of the community:

- The needs of the community appear to be low as there is no cost pressure envisaged with the addition of dulaglutide to formulary as cost compared to other available injectable GLP-1 receptor agonists is similar. In addition, all strengths of dulaglutide preparations are the same and as such no cost pressure expected from adding all available strengths to formulary.
- It is possible that availability of the higher strengths may avoid switching to an alternative and delay or reduce the introduction/combination with insulin which may avoid cost.

Equity and Equality:

- No impact anticipated.

The formulary application supports consistent, equitable access to treatment. Appropriateness of medicines for individual patients is a clinical decision by the prescribing clinician. There is no anticipated differential impact on people with protected characteristics.

Policy drivers:

Scottish Medicines Consortium

Dulaglutide (Trulicity®) is accepted for restricted use within NHS Scotland.
Indication under review: in adults with type 2 diabetes mellitus to improve glycaemic control as add-on therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
SMC restriction: as part of a triple therapy in patients with inadequate glycaemic control on two oral anti-diabetic drugs, as an alternative glucagon-like peptide 1 (GLP-1) agonist option.
Dulaglutide 1.5mg once weekly significantly reduced glycosylated haemoglobin (HbA1c) compared with a twice daily GLP-1 agonist and compared with a long-acting basal insulin analogue in patients with inadequate glycaemic control on two oral anti-diabetic drugs.
Dulaglutide is also indicated for adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. SMC has not reviewed dulaglutide in this indication and cannot recommend its use within NHS Scotland.[10]

All Wales Medicines Strategy Group

Dulaglutide (Trulicity®) is recommended as an option for restricted use within NHS Wales. Dulaglutide (Trulicity®) should be restricted for use in the following subpopulation / circumstances within its licensed indication for the treatment of type 2 diabetes in adults to improve glycaemic control:
After failure, intolerance or where there is a contraindication to, standard triple therapy (metformin and two other antidiabetic medicines) as an alternative to insulin therapy.
In combination with other glucose-lowering medicinal products but not including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control, in line with current NICE guidance.

Type 2 diabetes in adults: management. NICE guideline [NG28]

In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see recommendation 1.6.25) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:

triple therapy with:

- metformin, a DPP-4 inhibitor and a sulfonylurea or
- metformin, pioglitazone and a sulfonylurea or
- starting insulin-based treatment

More specifically, 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 body mass index (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.

Patients should 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 six months). See NICE evidence summary for more information.

Other CCG decisions:

1. **Mid Essex CCG (July 2019):** In combination therapy with metformin and a sulfonylurea, if triple therapy is not effective, not tolerated or contraindicated and the patient has:
   - a BMI of 35 kg/m2 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
   - has a BMI lower than 35 kg/m^2 and:
     - o for whom insulin therapy would have significant occupational implications or
     - o weight loss would benefit other significant obesity-related comorbidities.

   Patients should be informed of the goal of treatment when GLP-1 is initiated. Arrangements must be in place for a follow up in six months with a view to stopping if the HbA1c has not fallen by at least 1% (11mmol/mol) and a weight reduction of at least 3% has not been achieved. GLP-1 agonists should only be initiated in combination with insulin by a specialist team. Liraglutide (Victoza®) is the first choice daily GLP-1 for new starts, with Exenatide (Byetta) as an alternative daily injection choice. *Dulaglutide (Trulicity®) is the first choice for weekly GLP-1 preparations*.

2. **Bedfordshire and Luton CCGs (November 2020):** *Prescribing information sheet*: Dulaglutide 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.

   Overarching Shared Care Guideline for Glucagon-like peptide 1 (GLP 1) agonist: Joint first line choices:- Subcutaneous injection preparations of:-
   - Dulaglutide (Trulicity®)
   - Liraglutide (Victoza®) - NB maximum recommended dose of liraglutide is 1.2mg except in very exceptional circumstances and only after consultation with the Specialist Diabetes Team
3. **Oxfordshire CCG:** Dulaglutide(Trulicity®) First line option in line with updated GLP-1 receptor agonist guidelines (previously for those who would gain benefit from once weekly and can't have semaglutide).
4. **Crawley, Horsham and Mid Sussex CCGs:** Formulary: Dulaglutide (Trulicity®) has a green traffic light status and the indication is; treatment option for type 2 diabetes in line with NICE (NG28).

Implementability: No issues identified.

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