AWMSG Secretariat Assessment Report
Dulaglutide (Trulicity®▼) 1.5 mg and 0.75 mg solution for injection

This assessment report is based on evidence submitted by Eli Lilly and Company Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Dulaglutide (Trulicity®▼) is indicated in 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. 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[2].
Dosing	Monotherapy: the recommended dose is 0.75 mg once weekly. Add-on therapy: the recommended dose is 1.5 mg once weekly. For potentially vulnerable populations, such as patients aged 75 and over, 0.75 mg once weekly can be considered as a starting dose. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing[2].
Marketing authorisation date	21 November 2014[2]

2.0 DECISION CONTEXT

2.1 Background

Type 2 diabetes mellitus is a chronic metabolic condition, characterised by insulin resistance and insufficient insulin production, resulting in high blood glucose levels[3]. Diabetes is associated with long-term vascular complications, reduced quality of life and reduced life expectancy. People with diabetes also have an increased risk of cardiovascular disease[3]. Welsh Government statistics indicate that the prevalence of diabetes in Wales is 183,348 patients, of whom around 90% have type 2 diabetes[4,5].

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist[2]. In the presence of high blood glucose concentrations it stimulates beta cells in the pancreas to produce insulin, reducing blood glucose levels. Dulaglutide also slows gastric emptying and suppresses glucagon secretion, leading to reduced glucose output by the liver[2,6].

The National Institute for Health and Care Excellence (NICE) guideline on the management of type 2 diabetes in adults (NG28) places the GLP-1 agonists 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. The guideline specifies that the GLP-1 agonists are used in combination with metformin and a sulfonylurea for people with a BMI ≥ 35 kg/m^2 who have specific psychological or other medical problems associated with obesity, or for people with a BMI < 35 kg/m^2 for whom insulin therapy would have significant occupational implications, or for whom weight loss would benefit other significant obesity-related comorbidities[3,7]. NICE recommends only continuing GLP-1 agonist treatment if the person has had a beneficial metabolic response (a reduction of at least 1.0% (11 mmol/mol) in HbA_{1C} and

a weight loss of at least 3% of initial body weight in 6 months. NICE advise that a GLP-1 agonist should only be offered in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[7].

Unlike technology appraisals, NICE clinical guidelines are not mandated in Wales and therefore dulaglutide has been submitted for appraisal through AWMSG. The applicant company has requested that dulaglutide is considered for use in triple combination therapy in people whose diabetes is not adequately controlled by two oral antidiabetic agents, as an alternative treatment option to currently available GLP-1 agonists in Wales[1]. The company has not submitted evidence to support using dulaglutide as monotherapy or in combination with insulin[1].

2.2 Comparators

The comparators included in the company submission were:

- liraglutide
- lixisenatide
- once-weekly exenatide
- twice-daily exenatide[1].

2.3 Guidance and related advice

- NICE (2015) Type 2 diabetes in adults: management. NICE guideline NG28[3].
- NICE pathway (2015) Type 2 diabetes in adults[7].
- Scottish Intercollegiate Guidelines Network (SIGN) (2010; updated 2013) Management of diabetes. SIGN guideline 116[8].

The All Wales Medicines Strategy Group has previously issued a recommendation for restricted use of lixisenatide (Lyxumia®▼)[9]. Liraglutide (Victoza®) as part of a triple therapy regimen that does not include basal insulin and once-weekly exenatide (Bydureon®) have been appraised by NICE and subsequently this advice has been superseded by NG28[3,10]. In the absence of submissions from the marketing authorisation holders, liraglutide (Victoza®)[11] and twice-daily exenatide (Byetta®)[12] as a part of a regimen with basal insulin, are not endorsed for use in NHS Wales.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of three phase III studies directly comparing the effectiveness of dulaglutide with exenatide (AWARD-1), insulin glargine (AWARD-2), liraglutide (AWARD-6) or placebo (AWARD-1), and a network meta-analysis indirectly comparing dulaglutide with other comparator treatments[1]. AWARD-1 and -2 used dulaglutide in triple therapy. Despite insulin glargine not being a relevant comparator for the indication covered in this submission, data from AWARD-2 are included here because they provide evidence of dulaglutide in combination with metformin and a sulfonylurea, a more commonly used combination than the metformin and pioglitazone regimen used in AWARD-1. The AWARD-6 study will not be reported here because it was a study of dulaglutide in dual therapy and the company has requested consideration of dulaglutide for use in triple combination therapy[1]. In line with the licensed recommendations for dulaglutide as triple therapy, only the results from the 1.5 mg strength are reported below.

3.1 AWARD-1

AWARD-1 was a 52-week, multicentre, parallel-arm, randomised, open-label study that compared dulaglutide with exenatide or placebo, in 976 patients with type 2 diabetes taking maximally tolerated doses of metformin and pioglitazone[1,13]. Patients entering the study were ≥ 18 years, with a BMI of 23–45 kg/m^2 and HbA_{1c} concentrations of 7.0–11.0% (mean 8.1%; 65 mmol/mol). Patients were excluded if they were on long-term insulin therapy or were taking GLP-1 agonists during the 3 months before screening[13].

Patients were randomised 2:2:2:1 to one of four treatment arms: once-weekly dulaglutide 1.5 mg, once-weekly dulaglutide 0.75 mg, twice-daily exenatide 10 micrograms or once-weekly placebo[13]. Exenatide-treated patients received 5 micrograms twice daily for the first 4 weeks followed by 10 micrograms twice daily[13].

The primary endpoint, mean change in HbA_{1c} from baseline at 26 weeks, was statistically significantly improved for dulaglutide 1.5 mg-treated patients compared with exenatide-treated patients (see Table 1) [1,13]. Secondary endpoints (Table 1) showed significant improvement in mean HbA_{1c} at 52 weeks in the dulaglutide arm over the exenatide arm but no difference in mean change in body weight between these treatments at either 26 or 52 weeks[1,13]. Regarding quality of life (Table 1), there were no significant differences in change in EuroQol five dimensional (EQ-5D) index score from baseline for either the dulaglutide or exenatide arms[1]. Both dulaglutide and exenatide arms had significant improvements in EQ-5D visual analogue scale score from baseline, but differences between arms were not statistically significant. Patients treated with dulaglutide had a statistically significantly greater improvement in diabetes treatment satisfaction questionnaire score than exenatide-treated patients at both 26 and 52 weeks[1].

3.2 AWARD-2

AWARD-2 was a 78-week, multicentre, randomised, parallel-arm, open-label study in patients with type 2 diabetes taking maximally tolerated and stable doses of metformin and glimepiride[1,14]. This study compared once-weekly dulaglutide with once-daily insulin glargine (titrated to target)[1,14]. The key endpoints are included in Table 1; results are broadly similar to those in AWARD-1.

Table 1. Endpoints from AWARD-1[1,13] and -2[1,14]

AWARD-1	Dulaglutide 1.5 mg n=279	Exenatide 10 micrograms n=276	LS mean difference (95% CI)	p
Primary endpoint				
LS mean % change from baseline in HbA_{1c} (SE) at 26 weeks	−1.51 (0.06)	−0.99 (0.06)	−0.52 (−0.66 to −0.39)	<0.001
Secondary endpoints				
LS mean % change from baseline in HbA_{1c} (SE) at 52 weeks	−1.36 (0.08)	−0.80 (0.08)	−0.56 (−0.73 to −0.39)	<0.001
LS mean change in body weight (kg) (SE) at 26 weeks	−1.30 (0.29)	−1.07 (0.29)	-	0.474
Quality of life results				
EQ-5D: LS mean change from baseline (SE)	0.01 (0.01)	0.00 (0.01)		0.704
DTSQ: LS mean change from baseline (SE)	2.40 (0.34)	0.85 (0.33)		<0.001
AWARD-2	**Dulaglutide 1.5 mg n=273**	**Insulin glargine n=262**	**LS mean difference (95% CI)**	**p**
Primary endpoint				
LS mean % change from baseline in HbA_{1c} (SE) at 52 weeks	−1.08 (0.06)	−0.630 (0.06)	−0.45 (−0.60 to −0.29)	<0.001
Secondary endpoint				
LS mean change in body weight (kg) at 52 weeks	−1.87	1.44	-	<0.001

CI: confidence interval; DTSQ: diabetes treatment satisfaction questionnaire; EQ-5D: EuroQol five dimensional index score; LS: least squares; HbA_{1c} values can also be expressed in mmol/mol (see Glossary); SE: standard error.

3.3 Network meta-analysis

In the absence of studies directly comparing dulaglutide versus liraglutide, lixisenatide or once-weekly exenatide in the triple therapy setting, the company conducted a systematic review and network meta-analysis (NMA) to estimate the comparative clinical effectiveness of dulaglutide versus these comparators[1]. All studies included were randomised controlled trials of at least 16 weeks in duration conducted in adults with type 2 diabetes receiving at least two antidiabetic medicines. All included studies had outcomes of HbA_{1c} change from baseline and weight change from baseline. Treatment interventions included sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, GLP-1 agonists, and sodium-glucose co-transporter-2 inhibitors. The reference treatment for the NMA was placebo[1].

The base case analysis (used in the company's economic model, see Section 4) was based on a network containing a total of 48 studies ranging in duration from 16 to 36 weeks[1]. It showed a greater probability of dulaglutide being more effective in reducing HbA_{1c} than lixisenatide and twice-daily exenatide; and no significant difference in change in HbA_{1c} between dulaglutide, liraglutide and once-weekly exenatide[1]. Regarding change in weight, no difference was found between dulaglutide, lixisenatide, liraglutide, twice-daily exenatide and once-weekly exenatide[1].

An alternative analysis, stratifying for metformin and sulfonylurea co-treatment, showed that dulaglutide had a higher probability of reducing HbA_{1c} than twice-daily exenatide, liraglutide, once-weekly exenatide and lixisenatide[1]. However, this analysis used a smaller network and meta-regression did not adjust for baseline HbA_{1c}[1].

3.4 Comparative safety

The Committee for Medicinal Products for Human Use considered that overall the safety profile of dulaglutide was consistent with what has previously been observed in this class of medicines and separate analyses of areas of special interest did not reveal any unexpected findings or raise major concerns[6]. As expected for a GLP-1 agonist, the most common adverse events were gastrointestinal effects such as nausea, diarrhoea and vomiting[6]. The SPC describes an increased risk of hypoglycaemia in people receiving dulaglutide in combination with sulfonylurea or insulin and states that reducing the dose of sulfonylurea or insulin may lower this risk[2].

Significantly fewer patients in the dulaglutide arm than in the exenatide arm experienced hypoglycaemia in the AWARD-1 study[1,13]. In the AWARD-6 study there were no differences in the number of hypoglycaemic events in patients treated with dulaglutide and metformin versus those treated with liraglutide and metformin[15].

The network meta-analysis showed no difference between dulaglutide, lixisenatide, liraglutide, twice-daily exenatide and once-weekly exenatide regarding non-severe hypoglycaemia[1]. People taking dulaglutide had a higher probability of experiencing nausea compared with those on once-weekly exenatide. However, the probability of nausea was not different for patients treated with dulaglutide, liraglutide, lixisenatide or twice-daily exenatide[1].

3.5 AWTTC critique

- The applicant company has requested that dulaglutide is considered for use in triple combination therapy in people whose diabetes is not adequately controlled by two oral antidiabetic agents, as an alternative treatment option to currently available GLP-1 agonists in Wales[1]. However, the NICE guideline on managing type 2 diabetes in adults places the GLP-1 agonists at a later stage in the treatment pathway; after failure, intolerance or where there is a contraindication to, standard triple therapy of metformin and two other antidiabetic medicines[3]. The company comment that the updated NICE guideline was published around the time of the submission to AWMSG and

therefore the positioning was based on previous NICE guidance. However the company assert that this change does not affect the relative effectiveness of dulaglutide when compared to the other GLP-1 agonists and therefore will not affect the cost effectiveness results. They also comment that any changes in clinical practice following the NICE guidance would be expected to change prescribing of the GLP-1 agonists as a class.

- The NICE pathway for managing blood glucose in adults recommends that GLP-1 agonist treatment should only continue in people who have had a beneficial metabolic response, which includes a weight loss of at least 3% of initial body weight in six months. In the AWARD-1 study, patients lost around 1% of body weight after six months of treatment, which is less than the expected weight loss to continue on GLP-1 agonist treatment.
- Direct evidence has been provided for dulaglutide versus twice-daily exenatide; no studies have been conducted directly comparing dulaglutide in a triple therapy setting with liraglutide, lixisenatide or once-weekly exenatide. In the AWARD-1 study dulaglutide was compared to exenatide with a background of metformin and pioglitazone, however metformin and sulfonylurea would have been more representative of triple therapy used in Wales. A direct comparison versus insulin glargine in triple therapy has been provided but insulin glargine is not a relevant comparator[1].
- Lixisenatide is the only GLP-1 agonist recommended in Wales for use in combination with insulin[9]. The manufacturers of dulaglutide have not submitted evidence to support its use in combination with insulin[1] and once weekly exenatide is not licensed to be used in combination with insulin[16]. Therefore there are no once weekly GLP-1 agonists recommended in Wales for use in combination with insulin. Clinician feedback through the AWTTC clinical expert questionnaire raises the potential usefulness of being able to use a once weekly GLP-1 agonist for those patients on insulin therapy.
- Evidence indirectly comparing the clinical effectiveness of dulaglutide with liraglutide, lixisenatide or once-weekly exenatide has been provided using a network meta-analysis. Heterogeneity due to, for example, differences in patient baseline parameters and time to measurement of outcomes, reduced the reliability of comparison between treatments. Although the company has made some adjustments for heterogeneity, the adjustments may increase the uncertainty in the comparison. The literature search for the NMA was last updated in February 2015 and more recent publications are not included in the analysis[1]. In addition, the NMA included dual therapy studies which are less relevant to the indication under consideration. In general however, the methodology used was reasonable and the sensitivity analysis supports the base case analysis.
- Frequency of dosing may affect adherence to treatment. In a retrospective study investigating adherence to GLP-1 agonist therapy in 22,838 people with type 2 diabetes starting treatment, adherence was significantly higher for people starting once-weekly exenatide compared with those starting twice-daily exenatide or once-daily liraglutide[17]. However, this study did not include dulaglutide and the generalisability of the results to dulaglutide is not known.
- Dulaglutide is available as a single-use, disposable pen device with a pre-attached hidden needle[1]. Once-weekly exenatide needs to be reconstituted before injection[16]. Once-weekly dulaglutide may be more convenient for people to use and this may improve satisfaction and adherence to treatment. The single-use pen was not used in the AWARD studies, so its potential impact on quality of life compared with the ready-to use prefilled syringe which was used was not captured[1].
- The company conducted a discrete choice experiment in 243 adults with type 2 diabetes taking at least one oral antidiabetic medicine, who reviewed medication profiles representing the characteristics of dulaglutide and liraglutide[1]. Dosing frequency and type of delivery system were ranked as

important factors in choosing a GLP-1 agonist. More people preferred the dulaglutide profile (83%) than the liraglutide profile (16.9%)[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) of dulaglutide 1.5 mg used as a once-weekly subcutaneous injection as part of triple therapy in people whose type 2 diabetes is inadequately controlled by two oral antidiabetic drugs compared with other GLP-1 agonist alternatives available in Wales, including liraglutide 1.2 mg and 1.8 mg, lixisenatide, once-weekly exenatide and twice-daily exenatide[1]. The updated NICE guideline on managing type 2 diabetes in adults places the GLP-1 agonists at a later stage in the treatment pathway; after failure, intolerance or where there is a contraindication to, standard triple therapy of metformin and two other antidiabetic medicines[3]. The company comment that the updated NICE guideline was published around the time of the submission to AWMSG and therefore the positioning was based on previous NICE guidance. However the company assert that this change does not affect the relative effectiveness of dulaglutide when compared to the other GLP-1 agonists and therefore will not affect the cost effectiveness results.

The CORE diabetes model (CDM) is used to estimate the changes in total cost, total quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) over a 40-year time horizon (base case) from an NHS perspective. The CDM is a web-based diabetes policy analysis tool which can be adapted to different treatment options and uses real-time simulations, standardised risk equations and patient level data to estimate disease progression based on 15 inter-dependent Markov sub-models. It simulates progression of a variety of disease-specific complications (such as cardiac, arterial, ophthalmic and renal disease as well as ulcer and amputation), relevant physiological parameters (e.g. HbA_{1c}, systolic blood pressure, lipids and body mass index) and the modification of the risk factors by treatment and predicts patient outcomes accordingly. The model assumes that patients remain on GLP-1 agonist treatment in triple therapy for two years and are then switched to insulin glargine irrespective of treatment arm.

Clinical inputs for the model comprise HbA_{1c}, BMI, systolic blood pressure, cholesterol and triglycerides values as well as frequency of adverse events (nausea and hypoglycaemic events). The clinical data for the comparison of dulaglutide 1.5 mg and twice-daily exenatide were taken from the intention-to-treat population of the AWARD-1 study[13]. In the absence of direct comparisons between dulaglutide 1.5 mg and liraglutide (1.2 mg and 1.8 mg), lixisenatide and once-weekly exenatide, the company conducted a systematic review of the literature followed by a NMA using a Bayesian framework, which provided treatment response and tolerability data for these comparators for the model.

Cost data include treatment costs (including costs of medicines, costs associated with self-blood glucose monitoring and needles), health state costs (cost of co-morbidities such as myocardial infarction, stroke, eye complications, ulcer), and management costs (costs of statins, aspirin, ACE inhibitors etc., screening costs and nurse time). Costs of medicines have been obtained from MIMS[18] and other costs were taken from various publications between 2003 and 2015[1]. Utility values were taken from a recent systematic review of utility values for type 2 diabetes economic modelling[19]; disutilities are applied for adverse events/disease-related complications and quality of life is adjusted to account for patient preferences regarding administration frequency (+0.023 for once-weekly versus once-daily[20]) and administration device (+0.010 for dulaglutide prefilled pen versus other devices[21]).

Extensive deterministic sensitivity analysis as well as probabilistic sensitivity analysis is undertaken to account for uncertainties and limitations of the data and to test the robustness of the results to reasonable changes in values of key parameters.

4.1.2 Results

The results of the base case analysis are presented in Table 2. Dulaglutide 1.5 mg is reported to dominate all other GLP-1 agonist treatments used in Welsh clinical practice.

Table 2. Results of the base case analysis.

	Dulaglutide 1.5 mg	Liraglutide 1.2 mg	Difference†
Total costs	£28,327	£28,382	**−£55**
Total life-years	14.940	14.940	**0**
Total QALYs	7.853	7.809	**0.044**
ICER (£/QALY gained)	**Dulaglutide dominates**		
	Dulaglutide 1.5 mg	**Liraglutide 1.8 mg**	**Difference†**
Total costs	£28,327	£29,286	**−£959**
Total life-years	14.940	14.940	**0**
Total QALYs	7.853	7.809	**0.044**
ICER (£/QALY gained)	**Dulaglutide dominates**		
	Dulaglutide 1.5 mg	**Lixisenatide**	**Difference†**
Total costs	£28,327	£28,555	**−£228**
Total life-years	14.940	14.861	**0.079**
Total QALYs	7.853	7.716	**0.137**
ICER (£/QALY gained)	**Dulaglutide dominates**		
	Dulaglutide 1.5 mg	**Exenatide once-weekly**	**Difference†**
Total costs	£28,327	£28,330	**−£3**
Total life-years	14.940	14.932	**0.008**
Total QALYs	7.828	7.805	**0.023**
ICER (£/QALY gained)	**Dulaglutide dominates**		
	Dulaglutide 1.5 mg	**Exenatide twice-daily**	**Difference***
Total costs	£29,332	£29,879	**−£547**
Total life-years	15.794	15.752	**0.042**
Total QALYs	8.137	7.993	**0.144**
ICER (£/QALY gained)	**Dulaglutide dominates**		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
†Based on network meta-analysis
*Based on AWARD-1 study

Dulaglutide 1.5 mg remained the dominant treatment in most deterministic sensitivity analyses and results were insensitive to variations of time on treatment (one, three or five years), changes in time horizon, costs and most utilities. No QALY difference was found when treatment frequency utility was removed for the comparison with liraglutide (1.2 mg and 1.8 mg) and dominance was lost compared with lixisenatide when the upper HbA_{1c} change limit was used for dulaglutide (ICER = £68/QALY), time on treatment set to 5 years (ICER = £911/QALY) and time horizon reduced to 10 years (ICER = £1,201/QALY). Results in the comparison with once-weekly exenatide were mainly affected by treatment duration and time horizon with ICERs between £570 and £15,567 per QALY.

Probabilistic sensitivity analysis found dulaglutide 1.5 mg to be cost-effective in 100% of simulations at a £20,000/QALY threshold compared with liraglutide (1.2 mg and 1.8 mg), lixisenatide, and twice-daily exenatide, and 84% cost-effective against once-weekly exenatide.

The company also presents a cost-minimisation analysis which assumes all clinical and utility parameters to be equal. This estimates that dulaglutide 1.5 mg may result in annual cost savings of between £1.44 (compared with once-weekly exenatide) and £507 (compared with liraglutide 1.8 mg).

4.1.3 AWTTC critique

Strengths of the economic analysis are:

- The submission gives a very detailed and transparent account of the methods, data sources and analyses undertaken and the company acknowledges and addresses the main limitations by conducting extensive deterministic and probabilistic sensitivity analyses.
- The comparators included in the analysis appear appropriate as they include all licensed add-on therapies for the patient group of people with type 2 diabetes in need of triple therapy considering a GLP-1 agonist.
- The CDM is an externally validated and a regularly updated and reviewed web-based tool commonly used to assess health technologies for diabetes.
- The methodology of the systematic literature review and NMA informing the comparisons of dulaglutide versus liraglutide, lixisenatide and once-weekly exenatide appears robust and valid and the company acknowledges, and where possible, addresses any sources of bias and uncertainty.

Limitations of the economic analysis include:

- Clinical data for the 1-year cycles of the CDM for the NMA-based comparisons (liraglutide, lixisenatide and once-weekly exenatide) are based on 16-36 week outcome data because not enough data were available to inform the NMA for 37-56 week time points. This extrapolation of clinical data could introduce bias and potentially overestimate efficacy for these NMA-based comparisons because AWARD-1 showed less improvement compared with baseline at 52 weeks than at 26 weeks for both dulaglutide and twice-daily exenatide.
- The NMA was conducted to inform various HTA submissions and thus includes comparators that are not specific to this submission (e.g. insulin preparations). This would have increased heterogeneity and potentially resulted in bias.
- The AWARD-1 trial used metformin and pioglitazone in combination as background therapy. Considering that the combination of metformin and a sulfonylurea might be more common in Welsh practice, this could introduce uncertainty to the transferability of the results to the population of Wales. However, the company presents results for a sensitivity analysis based on an alternate NMA including patients with metformin and sulfonylurea background only which shows that dulaglutide dominates lixisenatide, exenatide once-weekly and liraglutide 1.8mg in this population.
- The publications included in the NMA did not provide sufficient data on BMI, and therefore weight was used to calculate BMI using average heights of the AWARD-1 and -2 populations. A number of assumptions and approximations regarding BMI were thus made, which could bias the effect of BMI on the outcomes of the model. However, the company argues that these uncertainties would be conservative for dulaglutide 1.5 mg.
- The model assumes that patients switch from a GLP-1 agonist to insulin glargine after two years. While in previous HTA submissions the switching point was set to five years, the company argues that a recent study has shown that average stopping time for GLP-1 agonist treatment in the UK is 1.5 years and that two years represents a conservative assumption[22].
- The company states that NHS reference costs are inappropriate because people with type 2 diabetes would be expected to have higher costs attached to conditions, such as angina, myocardial infarction or stroke, due to the more complicated case-mix. Therefore, other published cost data are used (some

from 2003[23]) and inflated to 2015 to inform the model. This could introduce bias into the analysis.

- In general, dulaglutide 1.5 mg dominates all other comparators in the base-case analysis, although differences in costs and QALYs are very small and the uncertainties around the key parameters could cause the results to shift. However, the company has addressed this in extensive sensitivity analyses which showed that dulaglutide 1.5 mg remained dominant and cost-effective in all analyses. Nevertheless, the company appreciates that the ICER is inherently unstable because of the small differences in cost and QALYs. The company tries to address this issue by also providing a cost-minimisation analysis comparing dulaglutide to exenatide once-weekly, liraglutide 1.2mg and liraglutide 1.8mg which estimates that dulaglutide 1.5 mg may result in annual cost savings of between £1.44 (compared with once-weekly exenatide) and £507 (compared with liraglutide 1.8 mg). However, in the absence of proof of equivalence, it is unclear whether the use of CMA is justified.
- The prefilled pen device used for dulaglutide 1.5 mg has the potential to save time spent training and assisting the patient with self-injection which could save NHS resources. While this has not been included in the analysis, it would increase the cost effectiveness of dulaglutide 1.5 mg relative to the comparators.

4.2 Review of published evidence on cost-effectiveness

A literature search did not identify any evidence of the cost-effectiveness of dulaglutide compared with the other GLP-1 agonists in a triple therapy setting within the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates a current prevalence of type 2 diabetes in Wales of 164,340 adults[1]. This is based on 182,600 people in Wales with diabetes[24] of whom 90% have type 2 diabetes[5]. It is assumed that the rate of diabetes remains constant over time and that there is an annual increase of 0.27% in the population of Wales[25.] This results in an expected 166,115 adults with type 2 diabetes by year five. An annual incidence rate of 515 new cases of diabetes per 100,000 population is applied based on 2010 figures[26]. Taking into account the annual population increase, this results in an estimated 12,715 new cases in year one (based on an adult population in Wales of 2,468,840[25]) increasing to 12,852 new cases in year five. The company assumes an annual mortality rate of 2.24% based on a mortality rate of people with type 2 diabetes that is 32% higher[27] than the standardised rate of 0.07% in Wales[28]. This results in a net number of people with type 2 diabetes of 173,090 in year one increasing to 174,960 in year five. Of these, 90% are on active treatment[29] of whom 6.6% will receive a GLP-1 agonist[1]. It is therefore estimated that there are currently 10,282 people taking GLP-1 agonists, and this figure is assumed to increase to 10,393 over the next five years. The company assumes the uptake of dulaglutide to be 4% in year one increasing to 25% in year five. This results in 246 people likely to receive dulaglutide 1.5 mg in year one and 1,554 in year five, taking into account an annual discontinuation rate of 39.8%[1].

5.1.2 Results

The estimated net budget impact is presented in Table 3. The company estimates that cost-savings of £1,316,705 could be made after introduction of dulaglutide over a five-year period, because the costs of the mainly displaced GLP-1 agonists are higher (market leader liraglutide 1.8 mg as well as liraglutide 1.2 mg) or similar (once-weekly exenatide) and no additional cost of needles is accrued.

Table 3. Company-reported costs associated with use of dulaglutide for the add-on treatment of type 2 diabetes.

	2016	2017	2018	2019	2020
Number of eligible patients (indication covered in this submission)	10,282	10,309	10,337	10,365	10,393
Uptake (%)	4%	9.5%	15%	20%	25%
Treated patients	411	979	1,551	2,073	2,598
Number of patients (less discontinuations)	246	586	927	1,240	1,554
Annual cost of dulaglutide	£234,996	£559,622	£885,993	£1,184,497	£1,484,586
Overall net budget impact[†]	-£33,095	-£173,809	-£272,675	-£370,328	-£466,797

[†] Cost savings across the entire eligible population treated with GLP-1 agonists if dulaglutide was introduced compared with a scenario without dulaglutide.

The company presents a sensitivity analysis which shows that cost savings increase if the discontinuation rate of dulaglutide decreases.

5.1.3 AWTTC critique

Strengths and weaknesses of the budget impact analysis are:

- The submission gives a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- Prevalence, incidence and mortality rates are assumed to remain constant over the five-year time horizon and uptake rates for dulaglutide are assumed by the company. The company states that the results were sensitive to changes in uptake rate. It is therefore unclear how realistic the forecasted budget impact is. The company has presented different uptake scenarios all of which confirm cost savings for dulaglutide. The company think, however, that the base case is most plausible and realistic:
    - Displacement of liraglutide 1.8mg, exenatide once-weekly and liraglutide 1.2mg (base case): cost savings £1,316,705
    - Displacement of liraglutide 1.2mg and 1.8mg in equal proportions (no impact on displacement of exenatide once-weekly): cost savings £887,534
    - Displacement of exenatide once-weekly and liraglutide 1.8mg and 1.2mg in equal proportions: cost savings £553,445
    - Displacement of exenatide once-weekly only: cost savings £162,631
- The budget impact analysis includes drug acquisition cost and costs of needles only. It does not include treatment effect-related costs or potential longer term resource savings.

5.2 Comparative unit costs

Annual acquisition costs for different treatment regimens used as add-on (triple therapy) treatments of type 2 diabetes are shown in Table 4.

Table 4. Examples of medicine acquisition costs for triple therapy for people with type 2 diabetes.

Regimens	Frequency and route of administration	Approximate annual cost per patient
Glucagon-like peptide-1 receptor agonists		
Dulaglutide (Trulicity®▼)	1.5 mg once weekly: subcutaneous injection	£956
Liraglutide (Victoza®)	0.6 mg, 1.2 mg or 1.8 mg once daily: subcutaneous injection	£955-£1,436
Lixisenatide (Lyxumia®▼)	20 micrograms once daily: subcutaneous injection	£756
Exenatide (Byetta®)	5 micrograms or 10 micrograms twice daily: subcutaneous injection	£831
Exenatide prolonged-release (Bydureon®)	2 mg once weekly: subcutaneous injection	£957
Not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details[2,16,30-32]. Costs are based on BNF list prices as of 26 January 2016, assuming vial wastage[33]. Cost of dulaglutide 1.5 mg supplied by company. Costs of administration and costs of needles are not included. This table does not imply therapeutic equivalence of drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, dulaglutide (Trulicity®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation or by Practitioners with a special interest in diabetes mellitus.

The company does not anticipate that dulaglutide (Trulicity®▼) will be supplied by a home healthcare provider.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 18 January 2016
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Glycated haemoglobin (HbA_{1c})

This reflects a person's blood glucose level. A higher HbA_{1c} level means more glucose has been present in the blood in the previous two to three months. Results are reported as a percentage or in mmol/mol (see Table 5)[34].

Table 5. Comparison of HbA_{1c} units[34]

HbA_{1c} (%)	HbA_{1c} (mmol/mol)
6.0	**42**
6.5	**48**
7.0	**53**
7.5	**58**
8.0	**64**
9.0	**75**

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