Type 2 diabetes: dulaglutide

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in June 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

For reducing HbA1c levels in people with type 2 diabetes, dulaglutide once weekly, when added to metformin, was statistically superior to exenatide twice daily (both in combination with pioglitazone), statistically superior to sitagliptin and statistically non-inferior to liraglutide 1.8 mg daily. As with the other glucagon-like peptide-1 (GLP-1) receptor agonists there are limited data from randomised controlled trials (RCTs) on the effect of dulaglutide on patient-oriented outcomes, such as rates of macrovascular or microvascular events, or on long-term safety.

Regulatory status: Dulaglutide (Trulicity) received a European marketing authorisation in November 2014 and was launched in the UK in January 2015.

Effectiveness	Safety
• Dulaglutide 1.5 mg or 0.75 mg once weekly was superior to placebo (treatment difference −11.5 mmol/mol [1.05% points] and −9.2 mmol/mol [0.84% points], respectively) and to exenatide twice daily (treatment difference −5.7 mmol/mol [0.52% points] and −3.4 mmol/mol [0.31% points], respectively) for change in HbA1c from baseline (1 RCT, n=978, 26 weeks). • Dulaglutide 1.5 mg or 0.75 mg once weekly was superior to sitagliptin once daily (treatment difference −7.8 mmol/mol [0.71% points] and −5.1 mmol/mol [-0.47% points] respectively) for change in HbA1c from baseline (1 RCT, n=1098, 52 weeks). • Dulaglutide 1.5 mg once weekly was non-inferior to liraglutide 1.8 mg once daily (treatment difference -0.66 mmol/mol [0.06% points]) for change in HbA1c from baseline (1 RCT, n=599, 26 weeks).	• According to the summary of product characteristics, the most common adverse events (1 in 10 people or more) are hypoglycaemia, particularly in combination with a sulfonylurea or insulin, and gastrointestinal disorders. • According to the European public assessment report (EPAR) possible long-term safety concerns of pancreatitis and pancreatic and thyroid cancers are consistent with other GLP-1 receptor agonists.
Patient factors	**Resource implications**
• Dulaglutide is given once weekly by subcutaneous injection. • The EPAR states that the overall effect of dulaglutide on weight was modest across the AWARD trials (mean changes 0.87 kg to 3.03 kg), and that the clinical relevance of the observed effect size with the 1.5 mg dose is uncertain. • According to the summary of product characteristics injection site reactions are uncommon with dulaglutide (more than 1 in a 1000 people to less than 1 in 100). • There are no comparative data with other weekly dose GLP-1 receptor agonists.	• The annual cost of dulaglutide 1.5 mg or 0.75 mg once weekly is £1182.35. • Annual costs for other GLP-1 receptor agonists range from £705.75 to £954.84 (excluding VAT; prices taken from Drug Tariff May 2015 or MIMS, May 2015).

Introduction and current guidance

The NICE guideline on type 2 diabetes states that managing type 2 diabetes is complex. It involves individualising a multifactorial approach, addressing blood pressure, blood lipids and lifestyle issues, as well as blood glucose. This guideline is being updated (date of publication to be confirmed). The GLP-1 receptor agonists exenatide, liraglutide and lixisenatide will be included in the update, but dulaglutide will not be included as the licence was not granted in time for inclusion in the scope of the guideline.

Full text of introduction and current guidance.

Product overview

Dulaglutide (Trulicity, Eli Lilly and Company) is a GLP-1 receptor agonist. It was launched in the UK in January 2015 for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in people 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.

The recommended dose is 0.75 mg once weekly as monotherapy and 1.5 mg once weekly as add-on therapy, by subcutaneous injection. A reduction in the dose of sulfonylurea or prandial insulin may be considered to reduce the risk of hypoglycaemia when dulaglutide is used in combination with these therapies.

For potentially vulnerable populations, such as people aged 75 years or older, 0.75 mg once weekly can be considered as a starting dose. For people with mild or moderate renal impairment no dose adjustment is necessary. Dulaglutide is not recommended for people with severe renal impairment (eGFR less than 30 ml/minute/1.73 m^2) or on dialysis.

Full text of product overview.

Evidence review

- Dulaglutide has been studied in 6 phase III randomised controlled trials (RCTs) in a broad population of people with type 2 diabetes. This evidence summary is based on 3 of the RCTs that have been published in full. These are AWARD 1 (Wysham et al. 2014), AWARD 5 (Nauck et al. 2014) and AWARD 6 (Dungan et al. 2014). Dulaglutide has been compared with insulin glargine in combination with metformin and glimepiride (AWARD 2, Giorgino et al. 2015), and in combination with prandial insulin lispro with or without metformin (AWARD 4, Blonde et al. 2015). Data from AWARD 2 and 4 studies included in the European public assessment report for dulaglutide (Trulicity) (EPAR) have been used to supplement data from the 3 published studies included in this evidence summary.

- In AWARD 1 (Wysham et al. 2014) 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.

- In AWARD 5 (Nauck et al. 2014) 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.

- In AWARD 6 (Dungan et al. 2014) 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).

- A weight reduction from baseline of between 0.87 kg and 3.03 kg was seen with dulaglutide 1.5 mg in the 6 RCTs in the AWARD programme. Weight loss with dulaglutide 1.5 mg once weekly was similar to that seen with exenatide 10 microgram twice daily and less than that seen with liraglutide 1.8 mg daily.

- The EPAR states that across the phase II and III integrated safety population (n=4006), the incidence of common events such as gastrointestinal (GI) disorders are consistent with those previously reported for other GLP-1 receptor agonists. The incidence of adverse events was

generally dose-related. In AWARD 1 (Wysham et al. 2014) the incidence of GI events was 47% in the dulaglutide 1.5 mg once weekly group and 42% in the exenatide 10 microgram twice daily group. In AWARD 6 (Dungan et al. 2014) the incidence was 36% in both the dulaglutide 1.5 mg once weekly and liraglutide 1.8 mg once daily groups.

- At the primary end point, the mean event rate of symptomatic hypoglycaemia was 0.34 events per person per year for dulaglutide 1.5 mg once weekly compared with 0.52 for liraglutide 1.8 mg daily (AWARD 6, Dungan et al. 2014) and the mean event rates were 0.45, 1.10, 1.47 and 0.37 events per person per year for dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide 10 microgram twice daily and placebo respectively in AWARD 1 (Wysham et al. 2014). According to the Trulicity summary of product characteristics incidences of documented symptomatic hypoglycaemia increased when dulaglutide was used in combination with a sulphonylurea (plus metformin) or with prandial insulin.

- The Trulicity summary of product characteristics states that injection site reactions are uncommon (incidence more than 1 in 1000 to less than 1 in 100). In AWARD 6 (Dungan et al. 2014) injection site reaction occurred in 0.3% of the dulaglutide group compared with 0.7% of the liraglutide group (at the highest dose) and 1 injection site reaction was reported in each of the dulaglutide 1.5 mg and exenatide groups in AWARD 1 (Wysham et al. 2014).

- The Trulicity summary of product characteristics states that small mean increases in PR interval (2 to 3 milliseconds from baseline compared with placebo) and a 2.4% incidence of first-degree atrioventricular block are observed with dulaglutide 1.5 mg in people with normal conduction at baseline. According to the EPAR, an event-driven cardiovascular outcome study is underway and is estimated to report in 2019.

- There are limited data on the use of dulaglutide in certain populations, such as people older than 75 years and people with renal or hepatic disease and heart failure. Long-term safety data are also limited; only 9% of the integrated phase II and III safety population quoted in the EPAR received dulaglutide for up to 2 years and less than half received the 1.5 mg dose.

- As with the other GLP-1 receptor agonists, there are limited data from RCTs of dulaglutide relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events. The evidence of efficacy relates solely to surrogate end points, chiefly reductions in HbA1c compared with a range of other agents, but not compared directly to other once weekly dosing GLP-1 receptor agonists. The clinical significance of the data needs to be considered in the context of the wider evidence base for the management of type 2 diabetes.

Full text of evidence review.

Context

Other currently licensed GLP-1 receptor agonists are exenatide, liraglutide and lixisenatide.

Dulaglutide is available as a 4-pre-filled pen pack (4 weeks supply) of 0.75 mg/0.5 ml pre-filled pens or 1.5 mg/0.5 ml pre-filled pens. Both strengths cost £90.95 per pack (excluding VAT; prices taken from MIMS, May 2015).

The annual cost of dulaglutide 0.75 mg or 1.5 mg once weekly is £1182.35. Annual costs for other GLP-1 receptor agonists range from £705.75 to £941.76. The other once weekly GLP-1 analogue is £818.88 per person per year (excluding VAT; prices taken from Drug Tariff May 2015 or MIMS, May 2015).

Full text of context.

Estimated impact for the NHS

The current NICE guidance on the management of type 2 diabetes recommends the use of the GLP-1 receptor agonists, exenatide or liraglutide in dual or triple therapy in certain circumstances. For continuing treatment beyond 6 months, the guideline recommends a reduction in HbA1c of at least 1.0% point (11 mmol/mol) and a weight loss of at least 3% of initial body weight. The results from AWARD 1, 5 and 6 suggest that dulaglutide 1.5 mg would achieve a reduction in HbA1c of at least 1.0% point (11 mmol/mol).

The HbA1c lowering effect of dulaglutide has been compared with various other blood glucose controlling treatments. Dulaglutide once weekly in combination with metformin and pioglitazone has been shown to be superior to exenatide twice daily and, in combination with metformin, superior to sitagliptin once daily and non-inferior to liraglutide 1.8 mg once daily, in reduction of HbA1c. However, the clinical significance of these treatment differences remains uncertain with respect to microvascular and macrovascular outcomes.

In the 3 RCTs reviewed in this evidence summary, weight loss with dulaglutide 1.5 mg once weekly was similar to that seen with exenatide 10 microgram twice daily and less than that seen with liraglutide 1.8 mg once daily.

The European public assessment report for dulaglutide (Trulicity) states that the incidence of common adverse events with dulaglutide is consistent with that previously reported for other

GLP-1 receptor agonists and the possible long-term safety concerns of pancreatitis and pancreatic and thyroid cancers are also the same.

Dulaglutide is given once weekly, which some people may prefer to the once or twice daily dosing of some other GLP-1 receptor agonists.

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

The NICE guideline on type 2 diabetes, which is being updated (date of publication to be confirmed) states that the management of type 2 diabetes is complex. It involves individualising a multifactorial approach, addressing blood pressure, blood lipids and lifestyle issues, as well as blood glucose. Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The NICE guideline on type 2 diabetes recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided. The Quality and Outcomes Framework (QOF) allocates points for achieving 3 levels of glucose control in people with type 2 diabetes: HbA1c of 75 mmol/mol (9%) or less, 64 mmol/mol (8%) or less and 59 mmol/mol (7.5%) or less.

In addition to dulaglutide, there are 3 other GLP-1 receptor agonists currently licensed and available in the UK: exenatide, liraglutide and lixisenatide. All are administered by subcutaneous injection. An evidence summary on lixisenatide for type 2 diabetes has been published.

The current NICE guideline on the management of type 2 diabetes and the NICE technology appraisals on liraglutide for the treatment of type 2 diabetes mellitus and exenatide prolonged-release suspension for the treatment of type 2 diabetes recommend the use of the GLP-1 receptor agonists, exenatide or liraglutide in dual or triple therapy in addition to metformin, a sulfonylurea or

a glitazone in certain circumstances (see the NICE guidance for more information). For continuing treatment beyond 6 months, a reduction in HbA1c of at least 11 mmol/mol (1.0% point) and a weight loss of at least 3% of initial body weight at 6 months is recommended.

Exenatide, liraglutide and lixisenatide will be included in the update of the NICE clinical guideline for the management of type 2 diabetes, but dulaglutide will not be included as the licence was not granted in time for inclusion in the scope of the guideline.

See the type 2 diabetes key therapeutic topic and the NICE pathway on diabetes for more information. See also the Clinical Knowledge Summary on type 2 diabetes for a general overview of prescribing considerations.

Product overview

Drug action

Dulaglutide (Trulicity) is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist with a half-life of 4.5 and 4.7 days for the 0.75 mg and 1.5 mg doses respectively, which makes it suitable for once-weekly subcutaneous administration.

Licensed therapeutic indication

Dulaglutide (Trulicity) is licensed for improving glycaemic control in adults with type 2 diabetes mellitus as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in people 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.

The safety and efficacy of dulaglutide has been evaluated in 6 phase III studies of people with type 2 diabetes as a monotherapy, in combination with 1 or 2 oral treatments (such as with metformin alone, metformin and a sulfonylurea, or metformin and pioglitazone) and in combination with prandial insulin. Dulaglutide has not been studied as add-on therapy in combination with sodium-glucose co-transporter 2 inhibitors. There is limited experience of dulaglutide when combined with basal insulin, thiazolidinediones or sulfonylureas alone, sulfonylureas plus

thiazolidinediones, and metformin plus sulfonylureas plus thiazolidinediones (European public assessment report product information: dulaglutide [Trulicity]).

Course and cost

For monotherapy the recommended dose is 0.75 mg once weekly, administered subcutaneously in the abdomen, thigh or upper arm region. The recommended dose is 1.5 mg once weekly when dulaglutide is used as add-on therapy. For potentially vulnerable populations, such as people aged 75 years or over, 0.75 mg once weekly can be considered as a starting dose as add-on therapy. No dose adjustment is needed in people with mild or moderate renal impairment. Dulaglutide is not recommended in people with severe renal impairment or on dialysis, as there is very limited experience of use in this group of people (Trulicity summary of product characteristics).

Dulaglutide is administered by a single-use pre-filled pen. The dose can be administered at any time of day, with or without meals. The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days (72 hours) before (Trulicity summary of product characteristics).

When dulaglutide is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When it is added to existing therapy of a sulfonylurea or prandial insulin, a reduction in the dose of sulfonylurea or insulin may be considered, to reduce the risk of hypoglycaemia. The use of dulaglutide does not require blood glucose self-monitoring. Self-monitoring may be necessary to adjust the dose of sulfonylurea or prandial insulin when dulaglutide is used as add-on therapy (Trulicity summary of product characteristics).

Dulaglutide is available as a 4-pre-filled pen pack (4 weeks supply) of 0.75 mg/0.5 ml pre-filled pens or 1.5 mg/0.5 ml pre-filled pens. Both strengths cost £90.95 per pack (excluding VAT; price taken from MIMS, May 2015).

Evidence review

Dulaglutide has been studied in 6 phase III randomised controlled trials (RCTs) in people with type 2 diabetes. These are:

- AWARD 1 – comparing dulaglutide (0.75 mg and 1.5 mg weekly) with exenatide (10 microgram twice daily) or placebo in people treated with background metformin and pioglitazone.

- AWARD 2 – comparing dulaglutide (0.75 mg and 1.5 mg weekly) with insulin glargine (once daily) in people treated with background metformin and glimepiride.

- AWARD 3 – comparing dulaglutide (0.75 mg and 1.5 mg weekly) with metformin (1500 mg to 2000 mg daily).

- AWARD 4 – comparing dulaglutide (0.75 mg and 1.5 mg weekly) with insulin glargine (once daily) in people treated with background prandial insulin lispro (3 times daily with [or without] metformin).

- AWARD 5 – comparing dulaglutide (0.75 mg and 1.5 mg weekly) with sitagliptin (100 mg daily) or placebo in people treated with background metformin.

- AWARD 6 – comparing dulaglutide (1.5 mg weekly) with liraglutide (1.8 mg once daily) in people already treated with background metformin.

This evidence summary is based on 3 of the RCTs that have been published in full. These are AWARD 1 (Wysham et al. 2014), AWARD 5 (Nauck et al. 2014) and AWARD 6 (Dungan et al. 2014). Information from the European public assessment report for dulaglutide (Trulicity, EPAR) has been used to clarify and supplement data from the 3 published studies included in this evidence summary. The monotherapy study, AWARD 3 (Umpierrez et al. 2014), AWARD 2 (Giorgino et al. 2015) and AWARD 4 (Blonde et al. 2015) have also been published but are not reviewed in this evidence summary. Data from these studies are given in the EPAR and are included in the integrated safety population. A number of other studies involving dulaglutide are also ongoing. The primary outcome measure in all the studies was glycosylated haemoglobin (HbA1c) change from baseline to the primary time point.

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).

- 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/m^2 (mean BMI 33 kg/m^2) 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 (1500 to 3000 mg per day) and pioglitazone (30 to 45 mg per day), people were randomised to 1 of 4 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 4 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.

Table 1 Summary of AWARD 1 (Wysham et al. 2014)

	Dulaglutide 1.5 mg	Dulaglutide 0.75 mg	Exenatide 10 micrograms twice daily	Placebo
Randomised	n=279	n=280	n=278	n=141
Efficacy[a]	n=279	n=280	n=276	n=141

Primary outcome: LS mean change ±SE in HbA1c from baseline to week 26[b]	−16.5±0.7 mmol/mol (1.51±0.06%) from baseline of 65.0±14 mmol/mol (8.1±1.3%) dulaglutide 1.5 mg compared with exenatide: LS mean change difference −5.7 mmol/mol (-0.52%) 95% CI −7.2 to −4.3 mmol/mol, p<0.001 for superiority	−14.2±0.7 mmol/mol (-1.30.±0.06%) from baseline of 65.0±13 mmol/mol (8.1±1.2%) dulaglutide 0.75 mg compared with exenatide: LS mean change difference −3.4 mmol/mol (-0.31%) 95% CI −4.8 to −2.0 mmol/mol, p<0.001 for superiority	−10.8±0.7 mmol/mol (-0.99±0.06%) from baseline of 65.0±14 mmol/mol (8.1±1.3%) exenatide compared with placebo: LS mean change difference −5.8 mmol/mol (-0.53%) 95% CI not reported, p<0.001 for superiority	−5.0±0.9 mmol/mol (0.46±0.08%) from baseline of 65.0±14 mmol/mol (8.1±1.3%) dulaglutide 1.5 mg compared with placebo: LS mean change difference −11.5 mmol/mol (1.05%) 95% CI −13.3 to −9.6 mmol/mol, p<0.001 for superiority dulaglutide 0.75 mg compared with placebo: LS mean change difference −9.2 mmol/mol (-0.84%) 95% CI −11.0 to −7.3 mmol/mol, p<0.001 for superiority
Selected secondary outcomes:				

LS mean change ±SE in eline to week 5HbA1c from bas2[b]	−14.9 ±0.9 mmol/mol (-1.36.±0.08%) dulaglutide 1.5 mg compared with exenatide: LS mean change difference -−6.1 mmol/mol (-0.56%) 95% CI not reported, p<0.001 for superiority	−11.7 ±0.9 mmol/mol (-1.07.±0.08%) dulaglutide 0.75 mg compared with exenatide: LS mean change difference -−3.0 mmol/mol (-0.27%) 95% not reported, p<0.001 for superiority	−8.8 ±0.9 mmol/mol (0.8 ±0.08%)	No analysis reported
People with HbA1c of less than 53 mmol/mol (7.0%) at week 26[b]	78% p<0.001 compared with exenatide and placebo	66% p<0.001 compared with exenatide and placebo	52%	43%
LS mean change ±SE in body weight from baseline to week 26[b]	−1.30 kg ±0.29 kg from baseline of 96 kg ±20 kg LS mean difference -0.24 kg, p<0.474 compared with exenatide	+0.2 kg ±0.29 kg from baseline of 96 kg ±21 kg LS mean difference +1.27 kg p<0.001 compared with exenatide	−1.07 kg ±0.29 kg from baseline of 97 kg ±19 kg p<0.001 compared with placebo	+1.24 kg ±0.37 kg from baseline of 94 kg ±19 kg dulaglutide 1.5 mg and 0.75 mg p<0.001 and p<0.010 respectively, compared with placebo
Safety[c]	n=279	n=280	n=276	n=141
Deaths at week 26	0.4% (1/279)	0.4% (1/280)	0%	0%

Serious adverse events at week 26	4% (12/279) No statistical analysis reported	5% (15/280)	5% (15/276)	9% (12/141)
Adverse events leading to withdrawal at week 26	3% (8/279)	1% (4/280)	3% (9/276)	2% (3/141)
Gastrointestinal adverse events at week 26	47% (131/279) p<0.001 compared with placebo	30% (83/280) p<0.05 compared with both exenatide and placebo	42% (117/276) p<0.001 compared with placebo	18% (26/141)
Total hypoglycaemia during 26 weeks[d]	10.4% p=0.007 compared with exenatide mean event rate= 0.45 events per patient per year	10.7% mean event rate= 1.10 events per patient per year	15.9% mean event rate= 1.47 events per patient per year	3.5% mean event rate= 0.37 events per patient per year

Abbreviations: CI, confidence interval; LS, least square, SE, standard error

[a] Modified intention-to-treat population: all participants who received at least 1 dose of study treatment.

[b] ANCOVA analysis with last observation carried forward.

[c] All participants who received at least 1 dose of study treatment.

[d] Hypoglycaemia with blood glucose of 3.9 mmol/l or less (with or without symptoms).

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

- Design: worldwide, multicentre, 104-week, randomised, double-blind and parallel group study with active control. Allocation was concealed.

- Population: 1098 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/m^2 (mean BMI 31 kg/m^2) 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 a 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 1 of the 4 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.

Table 2 Summary of <u>AWARD 5</u> **(Nauck et al. 2014)**

	Dulaglutide 1.5 mg	Dulaglutide 0.75 mg	Sitagliptin 100 mg daily	Placebo
Randomised	n=304	n=302	n=315	n=177
Efficacy[a]	Number of participants in each arm not reported			
Primary outcome: LS mean change ±SE in HbA1c from baseline to week 52[b]	−12.0±0.7 mmol/mol (1.10±0.06%) from baseline of 65.0±12 mmol/mol (8.1±1.1%) dulaglutide 1.5 mg compared with sitagliptin: LS mean change difference −7.8 mmol/mol (-0.71%) 95% CI −9.5 to −6.0 mmol/mol, p<0.001 for superiority	−9.5±0.7 mmol/mol (0.87±0.06%) from baseline of 66.0±12 mmol/mol (8.2±1.1%) dulaglutide 0.75 mg compared with sitagliptin: LS mean change difference −5.1 mmol/mol (-0.47%) 95% CI −6.9 to −3.4 mmol/mol, p<0.001 for superiority	−4.3±0.7 mmol/mol (-0.39±0.06%) from baseline of 65.0±12 mmol/mol (8.1 ±1.1%)	No data after week 26
Selected secondary outcomes:				

LS mean change ±SE in HbA1c from baseline to week 26[b]	−13.3±0.6 mmol/mol (1.22±0.05%) from baseline dulaglutide 1.5 mg compared with placebo: LS mean change difference −13.8 mmol/mol (-1.26%) p<0.001 compared with placebo and sitagliptin	−11.0±0.7 mmol/mol (1.01±0.06%) from baseline dulaglutide 0.75 mg compared with placebo: LS mean change difference −11.5 mmol/mol (-1.05%) p<0.001 compared with placebo and sitagliptin	−6.7±0.6 mmol/mol (-0.61±0.05%) from baseline sitagliptin 100mg compared with placebo: LS mean change difference −7.0 mmol/mol (0.64%) p<0.001	0.3±0.8 mmol/mol (0.03±0.07%) from baseline
People with HbA1c of less than 53 mmol/mol (7.0%) at week 52[b]	58% p<0.001 compared with sitagliptin	49% p<0.001 compared with sitagliptin	33%	No data after week 26
LS mean change ±SE in body weight from baseline to week 52[b] (placebo to 26 weeks)	−3.03 kg ±0.22 kg from baseline of 87 kg±17 kg LS mean difference -1.50 kg, p<0.001 compared with sitagliptin	−2.60 kg ±0.23 kg from baseline of 86 kg±18 kg LS mean difference -1.07 kg p<0.001 compared with sitagliptin	−1.53 kg ±0.22 kg from baseline of 86 kg±17 kg p<0.001 compared with placebo at week 26	+1.24 kg ±0.37 kg from baseline of 87 kg±17 kg dulaglutide 1.5 mg and 0.75 mg both p<0.001 compared with placebo at week 26
Safety[c]	n=304	n=302	n=315	n=177
Deaths at week 52 (placebo to 26 weeks)	0.3% (1/304)	0	0.6% (2/315)	0

Serious adverse events at week 52 (placebo to 26 weeks)	9% (26/304) No statistical analysis reported	5% (16/302)	5% (17/315)	3% (6/177)
Adverse events leading to withdrawal at week 52	11% (33/304)	8% (23/302)	10% (30/315)	No data after week 26
Gastrointestinal adverse events at week 52 (placebo to 26 weeks)	41% (126/304) p<0.001 compared with placebo at 26 weeks and sitagliptin at 52 weeks	37% (111/302) p<0.05 and p<0.001 compared with placebo at 26 weeks and sitagliptin at 52 weeks, respectively	23% (73/315)	23% (41/177)
Total hypoglycaemia during 52 weeks[d] (placebo to 26 weeks)	10.2% mean event rate= 0.4 events per patient per year	5.3% mean event rate= 0.3 events per patient per year	4.8% mean event rate= 0.1 events per patient per year	1.1% mean event rate= 0.1 events per patient per year

Abbreviations: CI, confidence interval; LS, least square; SE, standard error.

[a] Modified intention-to-treat population: all participants who received at least 1 dose of study treatment, had a baseline assessment and at least 1 post-baseline assessment of HbA1c. Due to missing HbA1c measurements, 13 participants did not contribute to the primary analysis but distribution of this missing data across treatment arms are not reported.

[b] ANCOVA analysis with last observation carried forward.

[c] All participants who received at least 1 dose of study treatment.

[d] Hypoglycaemia with blood glucose of 3.9 mmol/l or less (with or without symptoms).

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).

- Design: multicentre (9 countries in total from Europe, Mexico and USA), 26-week, <u>randomised</u>, open-label, parallel group study with active control. Randomisation was stratified by country and HbA1c. <u>Allocation was concealed</u>. Population: 599 adults (mean age 57 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 BMI of 45 kg/m^2 or less (mean BMI 33.6 kg/m^2) 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 (1500 mg or more per day) for 3 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 2-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 3 weeks).

  The study consisted of 26 weeks treatment and 4 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.

Table 3 Summary of <u>AWARD 6</u> (Dungan et al. 2014)

	Dulaglutide 1.5 mg once weekly	Liraglutide 1.8 mg once daily	Analysis

Randomised	n=299	n=300	
Efficacy[a]	n=299	n=300	
Primary outcome: LS mean change ±SE in HbA1c from baseline to week 26[b]	−16±0.55 mmol/mol (1.42±0.05%) from baseline of 65.0±8.8 mmol/mol (8.1±0.8%)	−15±0.55 mmol/mol (1.36±0.05%) from baseline of 65.0±8.8 mmol/mol (8.1±0.8%)	dulaglutide compared with liraglutide LS mean change difference: −0.66 mmol/mol (-0.06%) 95% CI −2.08 to +0.77 mmol/mol, p<0.0001 for non-inferiority
Selected secondary outcomes			
People with HbA1c of less than 53 mmol/mol (7.0%) at week 26[b]	68%	68%	No statistical analysis reported
LS mean change ±SE in body weight from baseline to week 26[b]	−2.90 kg (0.22 kg) from baseline of 93.8 kg (18.2kg) p<0.0001	−3.61 kg (0.22 kg) from baseline of 94.4 kg (19.0 kg) p<0.0001	dulaglutide compared with liraglutide LS mean difference: +0.71 kg 95% CI 0.17 to 1.26 p=0.011
Safety[c]	n=299	n=300	
Deaths at week 26	0	0	
Serious adverse events at week 26	2% (5/299)	4% (11/300)	p=0.13
Adverse events leading to withdrawal at week 26	6% (18/299)	6% (18/300)	p=0.99
Gastrointestinal adverse events at week 26	36% (107/299)	36% (107/300)	p=0.98

Total hypoglycaemia during 26 weeks[d]	9% (26/299) mean event rate= 0.34 events per patient per year	6% (17/300) mean event rate= 0.52 events per patient per year	No statistical analysis reported
Abbreviations: CI, confidence interval; LS, least square; SE, standard error.			
[a] Modified intention-to-treat population: all participants who received at least 1 dose of study treatment.			
[b] ANCOVA analysis with last observation carried forward.			
[c] All participants who received at least 1 dose of study treatment.			
[d] Hypoglycaemia with blood glucose of 3.9 mmol/l or less (with or without symptoms).			

Clinical effectiveness

The primary outcome measure in the AWARD 1, 2, 3, 4, 5 and 6 studies was HbA1c, a disease-orientated (surrogate) outcome. As with the other GLP-1 receptor agonists, there are limited data from trials of dulaglutide relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events. A further study investigating whether dulaglutide (compared with placebo) can reduce major cardiovascular events and other serious outcomes in people with type 2 diabetes when added to their anti-hyperglycaemic regimen is underway and estimated to report in 2019 (NCT01394952).

The European public assessment report for dulaglutide (Trulicity) (EPAR) considered 5 trials in the phase III study programme (AWARD 1, 2, 3, 4 and 5). This states that the included studies were adequately designed to investigate the use of dulaglutide in a broad population of people with type 2 diabetes as monotherapy and in combination with other treatment as double or triple therapy. The studies included people with type 2 diabetes of more than 2 years duration, with an average baseline HbA1c of more than 65 mmol/mol (8%) and most people had co-morbidities associated with type 2 diabetes. Treatment groups were well balanced with regards to baseline characteristics, although only 1.8% of participants were 75 years or older. Most people in the studies receiving metformin as background medication were on a daily dose of 1500 mg or higher, and dose distribution was balanced among treatment groups in each study.

The primary end point of the trials was the change in HbA1c from baseline in the modified intention-to-treat population. In AWARD 1 (Wysham et al. 2014), AWARD 5 (Nauck et al. 2014) and AWARD 6 (Dungan et al. 2014) the reduction with dulaglutide 1.5 mg from baseline HbA1c was 1.51% points, 1.10% points and 1.42% points respectively (see tables 1,2 and 3 for details). All active-controlled phase III studies were designed as non-inferiority studies and this was achieved

at the point of primary analysis. According to the EPAR dulaglutide 1.5 mg was also shown to be statistically significantly superior to the active comparator in AWARD 1, 2, 4 and 5, although only by a small margin in some cases.

- AWARD 1 (Wysham et al. 2014, see table 1 for details): mean treatment difference 5.7 mmol/mol (0.52% points, 95% CI 7.2 to 4.3 mmol/mol) and 3.4 mmol/mol (0.31% points, 95% CI 4.8 to 2.0 mmol/mol) with dulaglutide 1.5 mg and 0.75 mg once weekly respectively, compared with exenatide twice daily at 26 weeks (p<0.001 for superiority).

- AWARD 5 (Nauck et al. 2014, see table 2 for details): mean treatment difference 7.8 mmol/mol (0.71% points, 95% CI 9.5 to 6.0 mmol/mol) and 5.1 mmol/mol (0.47% points, 95% CI 6.9 to 3.4 mmol/mol) with dulaglutide 1.5 mg and 0.75 mg once weekly respectively, compared with sitagliptin 100 mg once daily at 52 weeks (p<0.001 for superiority).

- In AWARD 6 (Dungan et al. 2014, see table 3 for details) dulaglutide 1.5 mg was non-inferior but not superior to liraglutide 1.8 mg at 26 weeks: mean treatment difference 0.66 mmol/mol (0.06% points, 95% CI 2.08 to +0.77 mmol/mol; p<0.0001 for non-inferiority).

- See EPAR for the findings of AWARD 2 (Giorgino et al. 2015) and AWARD 4 (Blonde et al. 2015).

Statistically significantly more people achieved a HbA1c of less than 53 mmol/mol (7.0%) with both dosages of dulaglutide weekly compared with exenatide twice daily in AWARD 1 (Wysham et al. 2014; 78% and 66% with the 1.5 mg and 0.75 mg dosages respectively, compared with 52%, p<0.001 for both comparisons), and compared with sitagliptin once daily in AWARD 5 (Nauck et al. 2014; 58% and 49% with the 1.5 mg and 0.75 mg dosages respectively, compared with 33%, p<0.001 for both comparisons). However, when dulaglutide 1.5 mg once weekly was compared with liraglutide 1.8 mg once daily in AWARD 6 (Dungan et al. 2014; see table 3 for details), there was no difference between treatments; 68% of people in both groups achieved an HbA1c target of less than 53 mmol/mol (7.0%) at 26 weeks.

According to the EPAR, dulaglutide 1.5 mg was associated with a sustained weight reduction from baseline in 5 phase III studies; range 0.87 kg AWARD 4 (Blonde et al. 2015, at 26 weeks) to 3.03 kg AWARD 5 (Nauck et al. 2014, at 52 weeks). This weight loss did not always achieve statistical significance in comparative studies. In AWARD 1 (Wysham et al. 2014, see table 1 for details) the weight loss of people in the dulaglutide 1.5 mg group was not statistically significantly different compared with exenatide 10 microgram daily (mean difference 0.24 kg, p<0.474), and people taking exenatide statistically significantly lost more weight when compared with people taking dulaglutide 0.75 mg (mean difference 1.27 kg, p<0.001). In AWARD 5 (Nauck et al. 2014, see table 2 for details) people taking dulaglutide 1.5 mg and 0.75 mg statistically significantly lost more

weight compared to those in the sitagliptin group (mean difference 1.50 kg and 1.07 kg respectively, p<0.001) for both comparisons). In AWARD 6 (Dungan et al. 2014, see table 3 for details) people in the liraglutide 1.8 mg once daily group statistically significantly lost more weight than people in the dulaglutide 1.5 mg once weekly group (mean difference 0.71 kg, 95% CI 0.17 to 1.26, p=0.011).

Safety and tolerability

Safety data from the individual studies AWARD 1 (Wysham et al. 2014), AWARD 5 (Nauck et al. 2014) and AWARD 6 (Dungan et al. 2014) are given tables 1, 2 and 3 respectively.

The European public assessment report for dulaglutide (Trulicity) states that overall, the safety profile of dulaglutide appears consistent with what has previously been observed in this class. The EPAR gives safety data from the phase II and III integrated safety population, which included 4006 people given dulaglutide, 703 given placebo and 1541 given active comparators. A total of 2279 people (57%) continued dulaglutide treatment for 50 weeks or more but only 369 people (9%) took dulaglutide for up to 2 years and less than half received the 1.5 mg dose (n=1762). This data includes the 5 phase III RCTs (all of the AWARD programme of trials apart from AWARD 6 [Dungan et al. 2014], which compares dulaglutide with liraglutide). According to the Trulicity summary of product characteristics, in general, the adverse events reported in AWARD trials were transient and mild or moderate in severity. Across the safety population, the most frequent adverse events (1 in 10 people or more) were gastrointestinal disorders such as nausea, diarrhoea, vomiting and dyspepsia. Dulaglutide 1.5 mg once weekly had a higher incidence of gastrointestinal adverse events compared with dulaglutide 0.75 mg once weekly, for example nausea (21% and 13%), diarrhoea (14% and 11%) and vomiting (12% and 7%), which suggests gastrointestinal adverse events are dose related. Injection site reactions including erythema, or swelling at the injection site were uncommon (more than 1 in a 1000 people to less than 1 in 100).

The EPAR states that the incidence of common events such as gastrointestinal and injection site disorders with dulaglutide was consistent with those previously reported for other GLP-1 receptor agonists. In AWARD 1 (Wysham et al. 2014) the incidence of gastrointestinal adverse events with dulaglutide 1.5 mg once weekly was 47% compared with 42% in the exenatide 10 microgram twice daily group. In AWARD 6 (Dungan et al. 2014) the incidence of gastrointestinal events was 36% for both dulaglutide 1.5 mg once weekly and liraglutide 1.8 mg once daily. Incidence of nausea was slightly higher in the dulaglutide group (20%) compared with the liraglutide group (18%) but the difference was not statistically significant (p=0.46). In AWARD 6 (Dungan et al. 2014) injection site reaction occurred in 0.3% of dulaglutide group compared with 0.7% of liraglutide group and 1

injection site reaction was reported in both the dulaglutide 1.5 mg weekly and exenatide 10 microgram daily group in AWARD 1 (Wysham et al. 2014).

In the phase II and III integrated safety population, the EPAR looked at several specific adverse events, including hypoglycaemia, cardiovascular and cerebrovascular events, pancreatitis and cancer. The incidence of documented symptomatic hypoglycaemia was relatively low when dulaglutide was used as monotherapy (0.62 events per person per year with dulaglutide 1.5 mg compared with 0.09 events per person per year with placebo) or as an add-on to metformin (0.26 events per person per year with dulaglutide compared with 0.08 events per person per year with placebo). When dulaglutide was combined with a sulfonylurea or prandial insulin, the incidence of documented symptomatic hypoglycaemia increased but this was comparable to the incidence with active comparators (European public assessment report for dulaglutide (Trulicity). In AWARD 6 (Dungan et al. 2014) the mean event rate of hypoglycaemia was 0.34 events per person per year for dulaglutide 1.5 mg once weekly compared with 0.52 for liraglutide 1.8 mg, In AWARD 1 (Wysham et al. 2014) the mean event rates of hypoglycaemia were 0.45, 1.10, 1.47 and 0.37 events per person per year for dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide and placebo respectively at 26 weeks. Similar rates of hypoglycaemia were recorded in AWARD 5 (Nauck et al. 2014) for dulaglutide 1.5 mg (0.4) whereas events for dulaglutide 0.75 mg and sitagliptin were lower (0.3 and 0.1 events per person per year, respectively).There were no events of severe hypoglycaemia among dulaglutide-treated people in any of the AWARD 1, 5 or 6 studies, and 2 events were reported for exenatide-treated people in AWARD 1 (Wysham et al. 2014).

With regard to cardiovascular safety, according to the EPAR, across the phase II and III safety population the incidence of tachycardia was higher in people given dulaglutide than those on comparator treatment (0.7% and 0.3% respectively, p=0.056), as were syncope (0.4% and 0.2%, p=0.182) and hypotension (0.4% and 0.2%, p=0.101) but none of these differences were statistically significant. In AWARD 1 (Wysham et al. 2014), dulaglutide 1.5 mg and dulaglutide 0.75 mg were associated with statistically significant greater increases in heart rate at 26 weeks compared with exenatide and placebo (p< 0.05, all comparisons) but no differences between dulaglutide and exenatide were noted at 52 weeks. There were no clinically relevant changes in blood pressure between the 3 arms at 26 and 52 weeks. In AWARD 6 (Dungan et al. 2014) there were no statistically significant differences in heart rate or blood pressure between dulaglutide 1.5 mg weekly and liraglutide 1.8 mg daily. A myocardial infarction was reported in the liraglutide group.

The Trulicity summary of product characteristics also highlights that small mean increases in PR interval (2 to 3 milliseconds from baseline compared with placebo) and a 2.4% incidence of first-degree atrioventricular block are observed with dulaglutide 1.5 mg in people with normal

conduction at baseline. According to the EPAR, the exposure-adjusted incidence rates for treatment-emergent high PR interval in the safety population were: dulaglutide 21.5 per 1000 person years (73 people), exenatide twice daily 17.9 per 1000 person years (4 people), insulin glargine 10.3 per 1000 person years (6 people), metformin 4.9 per 1000 person years (1 person), placebo 25.9 per 1000 person years (7 people), and sitagliptin 11.3 per 1000 person years (7 people).

Pancreatitis has been identified previously as a safety issue with GLP-1 receptor agonists and all these products, including dulaglutide, have warnings in their summaries of product characteristics about a risk of developing acute pancreatitis. According to the EPAR, people with a history of acute or chronic pancreatitis were excluded from the dulaglutide studies, and actual and potential cases of pancreatitis during the clinical studies were recorded and analysed. Across the phase II and III studies 9 people developed acute or chronic pancreatitis with an incident rate of 1.4 people per 1000 person years for dulaglutide, compared with 3.5 for placebo and 4.7 for sitagliptin. There were no pancreatitis events for metformin, exenatide or insulin glargine. Two people developed pancreatic cancer who received dulaglutide; however, the EPAR states that these cases were unlikely to be associated with dulaglutide due to the limited exposure. Analysis of the incidence of malignant and unspecified tumours showed a similar incidence across treatment groups (European public assessment report for dulaglutide [Trulicity]).

The Trulicity summary of product characteristics states that there is limited experience of using dulaglutide in people with severe renal impairment or end stage renal disease and use in these groups is not recommended. It also states that there is limited experience of using dulaglutide in people with congestive heart failure.

Evidence strengths and limitations

As with the other GLP-1 receptor agonists, there are limited data from RCTs of dulaglutide relating to important patient-oriented outcomes, such as rates of macrovascular or microvascular events. The evidence of efficacy relates chiefly to reductions in HbA1c. The clinical significance of the data needs to be considered in the context of the wider evidence base for the management of type 2 diabetes.

The EPAR states that the design and conduct of the clinical programme was appropriate to assess the efficacy and safety of dulaglutide in a broad population of people with type 2 diabetes. There are some limitations in the data in the choice of active comparators used in some of the studies. For example the EPAR states that in AWARD 5 (Nauck et al. 2014), comparison with a sulphonylurea rather than sitagliptin may have been preferable; and that data regarding dulaglutide as an add-on

therapy to basal rather than prandial insulin are lacking. The specialists involved in the production of this evidence summary advised that studies with once weekly GLP-1 receptor agonists as comparators, rather than daily dosing comparators would be preferable in terms of a 'like for like' comparison. Similarly, they advised that liraglutide 1.2 mg is more commonly used in UK practice than liraglutide 1.8 mg, the active comparator in AWARD 6 (Dungan et al. 2014). This reflects NICE guidance on liraglutide for the treatment of type 2 diabetes mellitus and the EMA advice that the available evidence suggests only limited benefit on glycaemic control with the higher dose of liraglutide, with potentially an increased risk of adverse events (European public assessment report for Victoza, 2009). The ongoing AWARD research programme may address some of the gaps in the evidence with regards to the efficacy of dulaglutide. For example, a study considering the efficacy of dulaglutide in combination with insulin glargine (AWARD 9, NCT02152371) is ongoing with results expected in 2016.

The use of the ANCOVA method of analysis in all the clinical trials discussed in this evidence summary ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycaemic drugs and baseline HbA1c.

The investigators used the last observation carried forward (LOCF) approach to take account of missing data, which can affect the results. In this approach, the last available result for an individual is carried forward and analysed as though it were the result at the study end, regardless of when that person left the trial. According to the EPAR further sensitivity analyses provided reassurance that the handling of the missing data did not affect conclusions regarding efficacy and confirmed the robustness of the results.

The EPAR states that the baseline population contained few older people (only 1.8% were older than 75 years in AWARD 1 to 5) and excluded certain groups such as those with renal or hepatic disease and heart failure, which is a limitation of the data. Long term safety data were also limited as only 9% of the integrated phase II and III safety population received dulaglutide for up to 2 years and less than half received dulaglutide 1.5 mg (the most commonly used dose).

Context

Alternative treatments

Other currently licensed glucagon-like peptide-1 (GLP-1) receptor agonists are:

- exenatide

- Byetta 5 microgram and 10 microgram solutions for injection in prefilled pens (twice-daily use)

- Bydureon 2 mg powder and solvent for prolonged-release suspension for injection (once-weekly use)

- liraglutide

  - Victoza 6 mg/ml solution for injection in prefilled pen (once-daily use)

- lixisenatide

  - Lyxumia 10 microgram and 20 microgram solutions for injection in prefilled pens (once daily use)

See summaries of product characteristics for specific licensed indications.

Costs of alternative treatments

Drug and usual dosage[a]	Annual cost excluding VAT[b]
Dulaglutide 0.75 mg once weekly	£1182.35[c]
Dulaglutide 1.5 mg once weekly	£1182.35[c]
Exenatide 5 micrograms twice daily	£830.25[d]
Exenatide 10 micrograms twice daily	£830.25[d]
Exenatide 2 mg once weekly	£953.68[c]
Liraglutide 1.2 mg once daily	£954.84[c]
Lixisenatide 20 micrograms once daily	£705.75[c]

[a] The doses shown are taken from the relevant summary of product characteristics, but do not represent the full range that can be used nor do they imply therapeutic equivalence. Liraglutide is licensed at a dose of 1.8 mg once daily but this is not recommended in NICE technology appraisal guidance 203.

[b] Pack sizes differ among the GLP-1 receptor agonists. Yearly costs have therefore been calculated on the basis of cost per 365 days for medication administered each day, and cost per 52 weeks for medication given once-weekly.

[c] Prices taken from MIMS May 2015.

[d] Prices taken from Drug Tariff May 2015.

Estimated impact for the NHS

Likely place in therapy

NICE has not published guidance specifically related to dulaglutide, and this GLP-1 receptor agonist will not be included in the update of the NICE clinical guideline for the management of type 2 diabetes, (publication date to be confirmed).

The current NICE guideline on the management of type 2 diabetes and the NICE technology appraisals on liraglutide for the treatment of type 2 diabetes mellitus and exenatide prolonged-release suspension for the treatment of type 2 diabetes recommend the use of the GLP-1 receptor agonists exenatide or liraglutide in dual or triple therapy in addition to metformin, a sulfonylurea or a glitazone in certain circumstances (see the NICE guidance for more information). For continuing treatment beyond 6 months, the guideline recommends a reduction in HbA1c of at least 1.0% point (11 mmol/mol) and a weight loss of at least 3% of initial body weight.

In AWARD 1 (Wysham et al. 2014), AWARD 5 (Nauck et al. 2014) and AWARD 6 (Dungan et al. 2014) the reduction in HbA1c with dulaglutide 1.5 mg from baseline to the primary end point was 1.51% points, 1.10% points and 1.42% points respectively.

The HbA1c lowering effect of dulaglutide has been compared with various other blood glucose controlling treatments. In the 3 fully published RCTs reviewed in this evidence summary, dulaglutide (once weekly) in combination with metformin and pioglitazone has been shown to be statistically superior to exenatide (twice daily) at 26 weeks; and in combination with metformin, statistically superior to sitagliptin (once daily) at 52 weeks, in reduction of HbA1c. Dulaglutide 1.5 mg (once weekly) in combination with metformin has been shown to be statistically non-inferior to liraglutide 1.8 mg (once daily) at 26 weeks for the same primary outcome. However, the clinical significance of these treatment differences remains uncertain for patient-oriented outcomes, such as rates of macrovascular or microvascular events. Further studies in the AWARD programme have been published after the EPAR. These include a study investigating dulaglutide in combination with metformin and a sulfonylurea in comparison with insulin glargine (AWARD 2, Giorgino et al. 2015) and a study investigating dulaglutide (with or without metformin) in combination with insulin lispro in comparison with insulin glargine, (AWARD 4, Blonde et al. 2015).

Weight loss has been seen as a possible pleiotropic effect of GLP-1 receptor agonists, and is a criterion within NICE guidance for continuing treatment with exenatide or liraglutide in triple therapy in addition to metformin and a sulfonylurea beyond 6 months. The EPAR states that the overall effect of dulaglutide on weight was modest across the AWARD trials (mean changes 0.87 Kg

to 3.03 Kg), and that the clinical relevance of the observed effect size with the 1.5 mg dose is uncertain.

Overall, the EPAR states that the safety profile of dulaglutide is consistent with what has previously been observed for other GLP-1 receptor agonists, including the possible long-term safety concerns of pancreatitis and pancreatic and thyroid cancers. Dulaglutide is given once weekly, which some people may prefer to the once or twice daily dosing of some other GLP-1 receptor agonists. However, there are no direct comparison data with other weekly dosing GLP-1 receptor agonists. Dulaglutide is available as a fixed dose in a single-use, ready to use pre-filled pen which provides automatic dose delivery and no drug reconstitution is required before administration.

Estimated usage

The NHS prescription cost analysis for England 2014 reports that approximately 738,000 community prescriptions for GLP-1 receptor agonists were dispensed in 2014 at a cost of approximately £67 million (net ingredient cost).The manufacturer estimates that around 1950 people with type 2 diabetes (approximately 3% of those prescribed GLP-1 receptor agonists in quarter 3, 2014) will receive dulaglutide in 2015 (personal communication; Eli Lilly and Company).

Relevance to NICE guidance programmes

NICE has issued a guideline on type 2 diabetes, which is being updated (date of publication to be confirmed). Exenatide, liraglutide and lixisenatide will be included in the update of the NICE guideline for the management of type 2 diabetes. However, dulaglutide will not be included in this update as the licence was not granted in time for inclusion.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr TA Chowdhury has no relevant interests to declare.

Dr C Walton has recently received educational sponsorship to attend professional meetings from Abbott, Novo Nordisk, and Lilly UK.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

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