New Medicine Recommendations
Albiglutide (Eperzan®) and Dulaglutide (Trulicity®)
For Type II Diabetes Mellitus

Albiglutide: Black

Albiglutide is NOT recommended for use by the NHS in Lancashire. Data from the drug's clinical trial programme indicate that albiglutide may not consistently achieve the beneficial metabolic response target set by NICE in Guideline 28 for continued prescribing of GLP-1 agonists, defined as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months[1]

Dulaglutide: Green

Dulaglutide is a drug appropriate for initiation and ongoing prescribing in both primary and secondary care when prescribed in the following clinical circumstances (as described in NICE Guideline 28)[1]:

- after second intensification of therapy fails to achieve targets combined with metformin and a sulfonylurea if the patient:
  - has a BMI of ≥35 kg/m^2 **and** specific psychological or other medical problems associated with obesity (adjust accordingly for people from black, Asian and other minority ethnic groups) **or**
  - has a BMI < 35 kg/m^2 **and**
    - if insulin therapy would have significant occupational implications **or**
    - if weight loss would benefit other significant obesity related comorbidities

Or, with specialist care advice and ongoing support from a consultant-led multidisciplinary team:

- combined with insulin at second intensification of treatment in patients who cannot take metformin

Dulaglutide may only be continued if the person has a beneficial metabolic response, defined as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months

Details of Review

Name of medicine (generic & brand name):

a. Albiglutide (Eperzan®)
b. Dulaglutide (Trulicity®)

Strengths and forms:

a. Albiglutide - 30 mg and 50mg powder and solvent for solution for injection[2]
b. Dulaglutide - 0.75 mg and 1.5 mg solution for injection in pre-filled pen and solution for injection in pre-filled syringe[3]

Dose and administration:

a. **Albiglutide** - 30 mg once weekly, administered subcutaneously. The dose may be increased to 50 mg once weekly based on individual glycaemic response. When albiglutide is added to existing metformin therapy, the current metformin dose can be continued unchanged. It may be necessary to reduce the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycaemia when starting albiglutide.[2]

b. **Dulaglutide** - Monotherapy 0.75 mg once weekly, Add-on therapy 1.5 mg once weekly. For potentially vulnerable populations, such as patients ≥ 75 years, 0.75 mg once weekly can be considered as a starting dose. 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.[3]

BNF therapeutic class / mode of action: 6.1.2.3 Other antidiabetic drugs.[4] GLP-1 agonists.[5]

Licensed indication(s):

a. Albiglutide (Eperzan®) is indicated 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 patients for whom use of metformin is considered inappropriate due to contraindications or intolerance.
   - a**dd-on combination therapy** In combination with other glucose-lowering medicinal products including basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control[2]

b. Dulaglutide (Trulicity®) 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 i**n combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control[3]

Proposed use:

Only for use as described in NICE Guideline 28:[1]

- after second intensification of therapy fails to achieve targets combined with metformin and a sulfonylurea if the patient:
  - has a BMI of ≥35 kg/m^2 **and** specific psychological or other medical problems associated with obesity (adjust accordingly for people from black, Asian and other minority ethnic groups) **or**
  - has a BMI < 35 kg/m^2 **and**
    - if insulin therapy would have significant occupational implications **or**
    - if weight loss would benefit other significant obesity related comorbidities

Or, with specialist care advice and ongoing support from a consultant-led multidisciplinary team:

- combined with insulin at second intensification of treatment in patients who cannot take metformin

Albiglutide and dulaglutide may only be continued if the person has a beneficial metabolic response, defined as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months

Course and cost:

a. **Albiglutide** – both 30 mg and 50mg injections are priced at £71 per 4 week course, this equates to an **annual cost of £923.00**[5]

b. **Dulaglutide** – both 0.75mg and 1.5mg injections are priced at £73.25 per 4 week course, this equates to an **annual cost of £953.25**[6]

Current standard of care/comparator therapies: See extract from NICE guideline, below

Disease Background

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in hyperglycaemia. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

In 2013, over 3.2 million adults were living with a diagnosis of diabetes, with prevalence rates of 6% and 6.7% in England and Wales respectively. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Diabetes care is estimated to account for at least 5% of UK healthcare expenditure, and up to 10% of NHS expenditure.[1]

Initial Drug Treatment

NICE Guideline 28 consolidates several Technology Appraisals and Clinical Guidelines into one document addressing type 2 diabetes in adults. Additionally, there are 3 Technology Appraisals for the SGLT-2 inhibitors. NG28 lists the following initial drug treatment for type 2 diabetes:

- Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes.
- In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with:
    - a dipeptidyl peptidase-4 (DPP-4) inhibitor or
    - pioglitazone or
    - a sulfonylurea.

In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:

- reinforce advice about diet, lifestyle and adherence to drug treatment and
- support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and
- intensify drug treatment

First Intensification of Drug Treatment

Treatment with 2 non-insulin blood glucose lowering therapies in combination (dual therapy) Consider:

- Metformin plus DPP4-inhibitor
- Metformin plus pioglitazone
- Metformin plus sulfonylurea

- Metformin plus SGLT-2 inhibitor

If metformin is contraindicated or not tolerated. Consider:

- A DPP4-inhibitor, pioglitazone or a sulfonylurea
- Aim for HbA1c of 48 mmol/mol if using DPP4-inhibitor or 53 mmol/mol if using a sulfonylurea
- Pioglitazone plus a sulfonylurea

SGLT-2 inhibitors

Treatment of type 2 diabetes with combinations of medicines including SGLT-2 inhibitors is covered in three separate NICE Technology Appraisals: TA315 Canagliflozin in combination therapy for treating type 2 diabetes,[7] TA288 Dapagliflozin in combination therapy for treating type 2 diabetes[8] and TA336 Empagliflozin in combination therapy for treating type 2 diabetes.[9]

Dapagliflozin is recommended in combination with metformin and in combination with insulin, with or without other antidiabetic drugs. The guidance does not allow triple therapy outside a clinical trial.[8] The NICE recommendations for canagliflozin and empagliflozin are similar (slight differences in word ordering), allowing treatment in combination with metformin, in defined metformin containing triple therapies or in combination with insulin with or without other antidiabetic drugs.[7,9]

Second Intensification of Drug Treatment

Consider:

- Triple therapy with metformin plus DPP4-inhibitor plus a sulfonylurea
- Metformin plus pioglitazone plus a sulfonylurea
- Metformin plus pioglitazone or a sulfonylurea plus an SGLT-2 inhibitor

If metformin contraindicated or not tolerated. Consider:

- Insulin based treatment
- Only **offer a GLP-1 mimetic** in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team

Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months

Subsequent Treatment if Targets Not Achieved

If metformin based triple therapy is not achieving target**,** consider **triple therapy of metformin plus sulfonylurea plus GLP-1 mimetic** if the patient:

- has a BMI of ≥35 kg/m^2 and specific psychological or other medical problems associated with obesity (adjust accordingly for people from black, Asian and other minority ethnic groups) **and**
- specific psychological or other medical problems associated with obesity **or**
- has a BMI < 35 kg/m^2 and if insulin therapy would have significant occupational implications **or**
- If weight loss would benefit other significant obesity related comorbidities

Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months

The GLP-1 mimetics **exenatide** and **liraglutide** both had Technology Appraisals that were incorporated into NG28.

The LMMG approved **lixisenatide** for restricted use as an option only as add-on to basal insulin when a licensed GLP-1 mimetic is clinically indicated but twice daily exenatide may not be appropriate.[10]

Summary of efficacy data in proposed use:

As albiglutide and dulaglutide were licensed and marketed within a short time period, head to head data are not available. For both drugs, the clinical trial programmes were relatively comprehensive, albeit in different cohorts of patients. As with the other GLP-1 receptor agonists there are limited data from randomised controlled trials on the effect of albiglutide and dulaglutide on patient-oriented outcomes, such as rates of macrovascular or microvascular events, or on long-term safety.

Albiglutide Main Efficacy Studies

Albiglutide was reviewed by the Scottish Medicines Consortium,[11] which published its review on 11 January 2016, in the following setting:

- for use as the first injectable anti-diabetic medicine for patients with inadequate glycaemic control on oral anti-diabetic drugs, who are eligible for a GLP-1 agonist, and in whom once weekly administration is preferred.

This section of the New Medicine Assessment is based on the SMC's review of albiglutide.

Eight phase III studies recruited adults with type 2 diabetes mellitus not controlled, defined as glycosylated haemoglobin (HbA1c) 7% (but not exceeding 10%; 10.5% for HARMONY-6), on their anti-diabetic regimen, which varied across the studies. Randomisation was stratified by prior myocardial infarction (MI), HbA1c (<8.0% or 8.0%, except in HARMONY-1, no stratification, and HARMONY-6, <8.5% or 8.5%), age (<65 or 65years, except in HARMONY- 6), by background oral anti-diabetic drug (OAD) therapy in HARMONY-1, -4 and -6 studies and by renal impairment (mild, moderate or severe) in HARMONY-8. The equivalent mmol/mol values of HbA1c expressed in percentage points are: 6.5% ≡ 48mmol/mol, 7.0% ≡ 53 mmol/mol, 7.5% ≡ 58mmol/mol , 8.0% ≡ 64 mmol/mol and 8.5% ≡ 69 mmol/mol.[12]

Patients received albiglutide subcutaneous (SC) injection weekly or comparators. The primary endpoint was change from baseline in HbA1c at 26 weeks in studies HARMONY-6 and -8; at 32 weeks in HARMONY-7, at 104 weeks in HARMONY-3,[13] and at 52 weeks in the four other studies. The primary analyses were conducted in the intention to treat (ITT) population, which comprised all randomised patients who received at least one dose of study drug and had a baseline and at least one post-baseline HbA1c measurement, with last observation carried forward (LOCF) for missing data and data after rescue medication. Observed case analyses were also conducted to support the primary analyses.

For the primary outcomes, albiglutide significantly reduced HbA1c compared with placebo in HARMONY-1, -2, -3, and -5. Albiglutide was superior to glimepiride 2 to 4mg daily and sitagliptin 100mg daily in HARMONY-3 and superior to sitagliptin 25mg to 100mg in HARMONY-8. Albiglutide was inferior to pioglitazone 30 to 45mg daily in HARMONY-5 and inferior to liraglutide 1.8mg daily in HARMONY-7.[14] In HARMONY-4, which had a non-inferiority margin of 0.3%, albiglutide demonstrated non-inferiority to insulin glargine, and in HARMONY-6, which had a non-inferiority margin of 0.4%, albiglutide was non-inferior to pre-prandial insulin lispro.[15] These data are shown in the table, below, along with the secondary outcome, change from baseline in body weight. The European Medicines Agency considered albiglutide to be weight neutral.[16]

Table: Adjusted mean changes from baseline in HbA1c and body weight with differences between albiglutide and comparators at primary endpoint

	HbA1c (%)		Body weight (kg)	
	Mean	Difference*	Mean	Difference*
Monotherapy (HARMONY-2 at 52 weeks):				
Albiglutide 30mg weekly	-0.70	-0.83 (-1.11; -0.58)	-0.39	0.27 (-0.091; 1.46)
Albiglutide 50mg weekly	-0.89	-1.04 (-1.31; -0.77)	-0.86	-0.20 (-1.40; 1.01)
Placebo	0.15	-	-0.66	-
In combination with metformin (HARMONY-3 at 104 weeks)				
Albiglutide 30 to 50mg weekly	-0.63	-	-1.21	-
Glimepiride 2 to 4mg daily	-0.36	-0.27 (-0.45; -0.09)	1.17	-2.37 (-3.03; -1.71)
Sitagliptin 100mg daily	-0.28	-0.35 (-0.53; -0.17)	-0.86	-0.35 (-1.01; 0.31)
Placebo	0.27	-0.91 (-1.16; -0.65)	-1.00	-0.20 (-1.14; 0.73)
In combination with metformin ± sulphonylurea (HARMONY-5 at 52 weeks)				
Albiglutide 30 to 50mg weekly	-0.55	-	-0.42	-
Pioglitazone 30 to 45mg daily	-0.80	0.25 (0.10; 0.40)	4.43	-4.85 (-5.51; -4.20)
Placebo	0.33	-0.87 (-1.07; -0.68)	-0.40	-0.03 (-0.88; 0.82)
In combination with metformin ± sulphonylurea (HARMONY-4 at 52 weeks)				
Albiglutide 30 to 50mg weekly	-0.67	-	-1.05	
Insulin glargine at night	-0.79	0.11 (-0.04; 0.27)	1.56	-2.61 (-3.20; -2.02)
In combination with pioglitazone ± metformin (HARMONY-1 at 52 weeks)				
Albiglutide 30 to 50mg weekly	-0.81	-	0.28	-
Placebo	-0.05	-0.75 (-0.95; -0.56)	0.45	-0.18 (-1.15; 0.79)
In combination with basal insulin (HARMONY-6 at 26 weeks)				
Albiglutide 30 to 50mg weekly	-0.82		-0.73	
Insulin lispro pre-prandial	-0.66	-0.16 (-0.32; 0.00)	0.81	-1.54 (-2.09; -1.00)
In combination with various oral anti-diabetics (HARMONY-7 at 32 weeks)				
Albiglutide 50mg weekly	-0.78		-0.64	
Liraglutide 1.8mg daily	-0.99	0.21 (0.08; 0.34)	-2.19	1.55 (1.05; 2.06)
In patients with renal impairment (HARMONY-8 at 26 weeks)				
Albiglutide 30 to 50mg weekly	-0.83		-0.79	
Sitagliptin 25 to 100mg daily	-0.52	-0.32 (-0.49; -0.15)	-0.19	-0.60 (-1.14; -0.06)

Albiglutide – Commentary on Clinical Efficacy

In the HARMONY study programme, the primary outcome was change from baseline in HbA1c.[16] The equivalent of the HbA1c targets of 6.5% and 7.5% are 48mmol/mol and 58mmol/mol. Albiglutide as monotherapy and add-on to OADs significantly reduced HbA1c compared with placebo; the placebo-corrected reduction in most studies was approximately 0.8% to 1.0%.

In direct comparative studies, albiglutide was superior to glimepiride and sitagliptin but inferior to pioglitazone and liraglutide. It was non-inferior to insulin glargine, using a margin of 0.3%, and to insulin lispro, using a margin of 0.4%.[16] Within the positioning proposed by the company, as first injectable therapy in patients who are failing to respond to OADs, the most useful data derive from HARMONY-7 and HARMONY-4.

In HARMONY-7, albiglutide 50mg weekly was inferior to liraglutide 1.8mg daily in patients with diabetes that was uncontrolled on various OADs, which comprised dual therapy (mostly metformin and sulphonylurea) for 51% of patients, triple therapy for 7.4% and monotherapy for 41% (mostly metformin, 36%).

In HARMONY-4, albiglutide 30 to 50mg weekly was non-inferior to insulin glargine in patients with

diabetes that was uncontrolled on metformin ± sulphonylurea, with 82% of patients on metformin plus sulphonylurea at baseline.

In the HARMONY studies, the percentage of missing data for the primary endpoint increased as time of the endpoint increased and was larger for placebo groups. In the primary analysis, missing data were handled using LOCF, which may not be the most appropriate method. Within active groups, the percentage of missing data for HbA1c when this was primarily assessed at week 26 or week 32, was 17% to 31%; at week 52, was 32% to 42% (and 58% to 70% for placebo); and at week 104, was 46% to 55% (and 76% for placebo). The large amount of missing data may undermine reliability and confidence in the results.[16]

Three studies (HARMONY-4, -6 and -7) had an open-label design and this may compromise data for subjective outcomes and may affect discontinuation rates. Within the licensed indication, possible comparators would be all other anti-diabetic medicines. In accordance with NICE guidance, albiglutide is likely to be used as an option when patients fail to reach target on triple therapy, and in this context, comparators would include other GLP-1 agonists and basal insulins.

A Bucher indirect comparison of the effects of albiglutide 50mg weekly and exenatide ER 2mg weekly on HbA1c was performed. This supports an assumption of equivalence between these medicines, which underpins the cost-minimisation economic analysis. The comparison included data from the HARMONY-7 study[16,17] and the DURATION-6 study,[18] which both included a liraglutide 1.8mg daily treatment arm. The outcome included in the comparison was change in HbA1c from baseline to week 32 and week 26 in the respective studies. It concluded that albiglutide and exenatide ER have comparable efficacy in reducing HbA1c. Weaknesses of the comparison include differences across the studies in statistical analyses, especially with respect to handling missing data and differences in the treatment effect observed in the common comparator arm. Other relevant outcomes have not been formally assessed in the comparison e.g. change in body weight and rates of adverse events such as hypoglycaemia and injection-site reactions. There is also the possible omission of other studies that could have informed the comparison of relative treatment effects of these medicines.

Dulaglutide Main Efficacy Studies

Dulaglutide was reviewed by the Scottish Medicines Consortium,[19] which published its review on 11 January 2016, in the following setting:

- only for use as part of triple therapy in patients with inadequate glycaemic control on two oral anti-diabetic drugs (OADs) as an alternative to other GLP-1 agonists

This section of the New Medicine Assessment is based on the SMC's review of dulaglutide. NICE produced an evidence review for dulaglutide[20] which is slightly wider in scope than the SMC review. The SMC review, however, is more applicable to the New Medicine Assessment as it mainly considers evidence for use in the setting defined by NICE Guideline 28.[1]

Two studies (AWARD-1 and -2), which were open-label except for the comparison with placebo in the first, recruited adults with type 2 diabetes and inadequate glycaemic control defined as glycosylated haemoglobin (HbA1c) at least 7% (but not exceeding 11% on OAD monotherapy and 10% on OAD combination therapy). Patients entered lead-in periods where those not receiving specified OADs (i.e. metformin plus pioglitazone in AWARD-1 and metformin and glimepiride in AWARD-2) were switched from their existing OAD to these and doses up-titrated over two or four weeks in the respective studies and then maintained on stable doses for eight weeks. Patients with HbA1c greater than 6.5% after lead-in periods were randomised to study treatment, with stratification for country and HbA1c (≤8.5% or >8.5%).

In the AWARD-1 study patients were assigned to 52 weeks' treatment with dulaglutide 1.5mg or 0.75mg s/c once weekly; exenatide 5 micrograms s/c twice daily for 4 weeks then 10micrograms s/c twice daily; or placebo s/c once weekly for 26 weeks then dulaglutide 1.5mg or 0.75mg s/c once weekly. In the AWARD-2 study patients were randomised equally to 78 weeks' treatment with dulaglutide 1.5mg or 0.75mg s/c once weekly or insulin glargine once daily titrated to achieve

fasting plasma glucose <5.6mmol/L. The primary outcome was mean change in HbA1c from baseline to week 26 and 52 in the respective studies. This was assessed in the intention-to-treat population, which comprised all randomised patients who received at least one dose of study drug using analysis of covariance (ANCOVA) with last observations carried forward for missing data and time-points after administration of rescue medication. AWARD-1 was designed to test superiority to placebo then non-inferiority to active comparator. In both studies non-inferiority to active comparators was assessed using a 0.4% margin.[21,22,23]

In AWARD-1 least squares (LS) mean changes from baseline to week 26 in HbA1c with dulaglutide 1.5mg, dulaglutide 0.75mg, exenatide and placebo were -1.51%, -1.30%, -0.99% and -0.46%, respectively. These were significantly greater for dulaglutide 1.5mg and 0.75mg compared to placebo with differences of -1.05% and -0.84%; and compared to exenatide, with differences of -0.52% and -0.31% respectively. LS mean change in body weight from baseline to week 26 was -1.30kg, 0.20kg, -1.07kg and 1.24kg in the dulaglutide 1.5mg and 0.75mg, exenatide and placebo groups, respectively.

In AWARD-2 LS mean changes from baseline to week 52 in HbA1c with dulaglutide 1.5mg, dulaglutide 0.75mg and insulin glargine were -1.08%, -0.76%, and -0.63%, respectively. Non-inferiority was demonstrated for both doses of dulaglutide compared to insulin glargine, and dulaglutide 1.5mg was also superior. Differences compared to insulin glargine were -0.45% for dulaglutide 1.5mg and -0.13% for dulaglutide 0.75mg. Mean change in body weight from baseline to week 52 was significantly different in the dulaglutide 1.5mg and dulaglutide 0.75mg groups compared to insulin glargine: -1.87kg and -1.33kg versus 1.44kg, respectively.[3,23]

In AWARD-1 and -2 there was little change from baseline and generally no consistent significant differences between active treatments for EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and visual analogue scale of current health state. In AWARD-1 at 52 weeks mean change from baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ)-status score and the similar mean DTSQ-change score (both on 36-point scales) were significantly greater with dulaglutide 1.5mg compared to exenatide, with between treatment differences of 1.37 and 1.35 on the respective scales. DTSQ-status and DTSQ-change items 2 and 3 assess patients' perceptions of frequency of hyperglycaemia and hypoglycaemia on 6-point scales, respectively. In the AWARD-1 study there were significant differences on both scales between dulaglutide 1.5mg and 0.75mg versus exenatide for item 2 (hyperglycaemia), which were typically less than 0.8 points; and for item 3 (hypoglycaemia), on mean change in DTQS-status score only, which was less than 0.4 points.[23,24]

Evidence was also provided from a supportive study with metformin monotherapy as the baseline therapy. In the supportive AWARD-6 study, which was an open-label non-inferiority study, 599 adults with type 2 diabetes inadequately controlled on metformin were randomised to dulaglutide 1.5mg s/c once weekly or liraglutide 1.8mg s/c once daily for 26 weeks. The primary outcome, LS mean change from baseline to week 26, was -1.42% and -1.36% in the respective groups, with a difference of -0.06%, which was within the pre-specified margin for noninferiority of 0.4%. Mean reduction in body weight at week 26 was 2.90kg and 3.61kg respectively, with a difference between groups of 0.71kg (p=0.011).[3,25]

Dulaglutide – Commentary on Clinical Efficacy

For triple therapy use, relevant data are derived from the AWARD-1 and AWARD-2 studies in patients who had inadequate glycaemic control on dual OAD therapy: metformin plus pioglitazone and metformin plus glimepiride in the respective studies. The background dual OAD therapy in AWARD-2 was considered representative of many patients in NHS Scotland. However the active comparator in AWARD-2, insulin glargine, is not relevant to use as an alternative to other GLP-1 agonists. Dulaglutide 1.5mg significantly reduced HbA1c, compared to exenatide twice daily in AWARD-1, by about 0.5% at 26 weeks; and, compared to insulin glargine in AWARD-2, by about 0.45% at week 52. Supportive data were provided from the AWARD-6 study in patients with inadequate glycaemic control on metformin monotherapy, indicating that dulaglutide 1.5mg and

liraglutide 1.8mg similarly reduced HbA1c at 26 weeks.[23]

There are no direct comparative data for dulaglutide 1.5mg and the GLP-1 agonists, exenatide ER, liraglutide (1.2mg and 1.8mg) or lixisenatide in patients with inadequate glycaemic control on two OAD. To address this, results for comparisons of GLP-1 agonists derived from a Bayesian network meta-analysis (NMA) were provided. These suggested that dulaglutide was at least comparable to other GLP-1 agonists and potentially superior to some, such as exenatide twice daily. Data from the NMA comparing GLP-1 agonists to placebo for change from baseline in HbA1c and body weight were applied to the economic evaluation. The NMA was weakened by heterogeneity in a number of areas including time-points for outcomes input to the analysis, definitions of non-severe hypoglycaemia, and treatment effect in the common control arms. Also Bayesian analyses were interpreted using frequentist significance[a].

The primary outcome in the AWARD-1, -2 and -6 studies was mean change from baseline in HbA1c. This is an established measure of blood glucose control over the preceding two to three months. The way in which HbA1c results are expressed in the UK has changed: results are now reported as mmol/mol rather than as a percentage. The open-label design of AWARD-1 and AWARD-2 studies may limit assessment of subjective patient-reported outcomes such as adverse events and quality-of-life assessments, including the DTSQ questionnaire. There was no evidence presented for validation of the DTSQ and the clinical significance of differences with dulaglutide relative to placebo and exenatide of 2 points on 36-point scales for DTSQ-status and DTSQ-change and of <0.70 points on 6-point scale for perception of hyperglycaemia is unknown. In the overall clinical study programme (phase II and III studies) there were only 115 (1.9%) patients aged >75 years and patients with significant renal or hepatic disease or advanced heart failure were excluded from the studies.[23]

The AWARD-1 and AWARD-2 studies recruited patients previously receiving OAD monotherapy or combination therapy. Patients on OAD monotherapy or on three or more OAD at baseline were stabilised for eight weeks on two OAD during the lead-in period before commencing a third agent. These treatment paths may not be representative of usual clinical practice. In the respective studies 25% and 16% of patients were on OAD monotherapy at screening while 23% and 18% of patients were receiving more than two OAD at screening.[23,21,22]

Clinical experts consulted by SMC consider that the place in therapy of dulaglutide is as an alternative to other GLP-1 agonists and a further once-weekly option. In comparison to exenatide ER, the licensed indications for dulaglutide are broader to include use in combination with insulin and as monotherapy. Unlike exenatide ER, dulaglutide is licensed for use without dose adjustments in patients with moderate renal impairment. It was also noted that dulaglutide was available via an automated injection device which may be easier for needle phobic patients.

Summary of safety data:

Albiglutide

In general, the adverse event profile of albiglutide is similar to other GLP-1 agonists, with gastro-intestinal events commonly reported. In the comparison to liraglutide (HARMONY-7), nausea was less frequently reported by those receiving albiglutide compared to liraglutide: 10% versus 29%, respectively. Injection-site reactions (ISR) are also reported with GLP-1 agonists and in HARMONY-7 these were significantly more frequent in the albiglutide group compared with liraglutide: 6.9% versus 1.2%. In analysis that included the term ISR and other related terms, albiglutide was associated with higher frequencies of events than other injected therapies: 13% versus 5.4% for albiglutide compared to liraglutide; 9.5% versus 5.3% for albiglutide versus insulin lispro; and 17% versus 10% for albiglutide versus insulin glargine. In the integrated safety

[a] Frequentist probability is a standard interpretation of probability; it defines an event's probability as the limit of its relative frequency in a large number of trials.

database, the main adverse event that led to treatment discontinuation in the albiglutide group, which occurred at a higher rate than with placebo, was ISR. In this database, the incidence of pneumonia was significantly higher with albiglutide versus all comparators: 1.75% versus 0.79%; this imbalance was noted across all individual studies.[11]

Rates of hypoglycaemia when albiglutide was used as monotherapy were low. However, these increased when it was used in combination with sulphonylurea or insulin. Rare, but more serious, adverse events associated with GLP-1 agonists include intestinal obstruction and acute pancreatitis. Pancreatic and thyroid cancers are also noted as potential safety issues and monitored in pharmacovigilance activities.[16]

In an integrated analysis of data from the eight phase III studies, atrial fibrillation or flutter occurred more frequently in the albiglutide group than in the comparators groups: 1.3% versus 0.5%. A case review did not provide an explanation for this. Albiglutide is also associated with a dose-dependent increase in heart rate. Transient ischaemic attack occurred in a larger proportion of patients given albiglutide than all comparators: 0.6% versus 0.2%, respectively. Cerebrovascular accident occurred in 0.33% and 0.18% of patients in the respective groups. However, atrial fibrillation prior to TIA or CVA was noted for only 2 of the 20 reported cases. The incidence of first major adverse cardiovascular event was similar in the albiglutide group versus the all comparators group, 1.2 versus 1.1 per 100 patient-years, respectively.[16]

Dulaglutide

The adverse event profile of dulaglutide is consistent with that of a GLP-1 agonist. In AWARD-1 within the dulaglutide 1.5mg once weekly and exenatide twice daily groups there were similar rates at 26 weeks of adverse events (77% and 72%); serious adverse events (4.3% and 5.4%); gastro-intestinal adverse events (47% versus 42%); nausea (28% versus 26%); vomiting (17% versus 11%) and diarrhoea (11% versus 6%). Hypoglycaemia, defined as plasma glucose of 3.9mmol/L or less and/or symptoms of hypoglycaemia was reported by 10% versus 16%, respectively, at 26 weeks (p=0.007); and by 12% versus 18% at 52 weeks. Mean increases in pancreatic enzymes (p-amylase, total amylase and lipase) were greater for dulaglutide 1.5mg than exenatide twice daily at 26 weeks and were greater for total amylase and p-amylase at 52 weeks. The incidence of patients with elevations of pancreatic enzymes above the upper limit of normal during treatment was similar across the groups. [2,19,21,23]

In the AWARD-2 study rates of overall and serious adverse events were similar across the groups through to week 78. At 78 weeks dulaglutide 1.5mg, compared to the insulin glargine, was associated with increased rates of nausea (15% versus 1.5%) and diarrhoea (11% versus 5.7%). The incidence of total hypoglycaemia at 78 weeks was 59% and 71% in the respective groups; and of severe hypoglycaemia was 0.7% and 0.8%, respectively. Both doses of dulaglutide were associated with increases in pancreatic enzymes from baseline, which were significant versus insulin glargine for p-amylase, total amylase and lipase. The proportions of patients with normal levels at baseline who had an elevation of these liver enzymes above the upper limit of normal was significantly greater in both dulaglutide groups compared to insulin glargine. [2,23]

In AWARD-6 within the dulaglutide 1.5mg and liraglutide 1.8mg groups there were similar rates of overall (62% and 63%), serious (2% and 4%); and gastro-intestinal adverse events (36% and 36%), including nausea (20% and 18%), diarrhoea (12% and 12%), vomiting (7% and 8%). Hypoglycaemia was reported by 8.7% (26/299) and 5.7% (17/300) of patients in the respective groups.[3,25]

Across the clinical study programme the incidence of injection site reactions with dulaglutide was low and noted by the regulatory authority to be similar to other agents in the class. Within the class of incretin mimetics, serious pancreatic adverse events, pancreatitis and pancreatic cancer, have been identified by the regulatory authority as potential risks. In common with other GLP-1 agonists dulaglutide has cardiovascular effects, such as reducing blood pressure and increasing heart rate. The clinical relevance of these is uncertain and being investigated in an ongoing

study.[23]

Strengths and limitations of the evidence:

Strengths:

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

Limitations

- As with the other GLP-1 receptor agonists, there are limited data from RCTs of albiglutide or 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.
- 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
- 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.
- The baseline populations contained few older people and excluded certain groups such as those with renal or hepatic disease and heart failure.
- Long term safety data are limited

Summary of evidence on cost effectiveness:

Albiglutide

Albiglutide's manufacturer submitted a cost-minimisation analysis to the SMC comparing albiglutide with exenatide ER for the selective positioning as a third-line, first injectable medicine for patients with type 2 diabetes who are uncontrolled on OADs, and for whom once-weekly administration is preferable. Based on SMC clinical experts' responses the comparator seems appropriate. A one-year time horizon was used and the analysis was carried out from an NHS Scotland perspective. The sensitivity analysis explored three and five year time horizons.[11]

No direct clinical studies comparing albiglutide and exenatide ER were identified by the submitting company and, therefore, a Bucher indirect comparison of albiglutide and exenatide ER, as described above, was conducted to support the cost-minimisation analysis. The results of the indirect comparison suggested that comparable efficacy had been demonstrated between albiglutide and exenatide ER.

The only costs included by the submitting company were drug acquisition costs per patient per year. In the first year, the base case results showed estimated savings associated with albiglutide of £31 per patient assuming all patients receive the 50mg dose. The analysis showed albiglutide has comparable efficacy to exenatide ER and, based on this assumption, it is a cost-effective treatment option. Therefore, the economic case has been demonstrated[11] .

Dulaglutide

Dulaglutide's manufacturer presented a cost minimisation analysis (CMA) to the SMC of dulaglutide as part of triple therapy compared to the other GLP-1 agonists liraglutide (1.2mg and 1.8mg and at an average daily dose of 1.53mg) and exenatide ER in patients inadequately controlled on two OADs as an alternative to currently available GLP-1 agonists. A cost-utility analysis (CUA) was also presented against lixisenatide and exenatide twice daily in the same

population. As such, the company was not seeking acceptance for the medicine as monotherapy, dual therapy or in combination with insulin. The company considered the main comparator to be liraglutide based on prescribing patterns.[19]

The CMA used a one year time horizon and considered only costs relating to the medicines and the cost of needles. The evidence supporting the comparability of the medicines came from the indirect comparisons described above. While differences existed between dulaglutide and exenatide ER in terms of nausea and injection site reactions (the former being greater with dulaglutide and the latter being greater with exenatide ER), no differences were assumed in the analysis for the sake of simplicity and to allow the selection of a CMA approach.

For the CUA, a lifetime (40 year) time horizon was used and the analysis used the CORE diabetes modelling structure[26,b] which is designed to determine the long-term health effects of treatments for diabetes by using epidemiological evidence on physiological markers to link to long term outcomes (e.g. renal complications, cardiovascular events, micro-vascular complications).

The clinical evidence on the key treatment effects of HbA1c and weight change in the CUA was taken from two sources. For the comparison with exenatide twice daily, data were taken from the AWARD1 study. However, for the comparison with lixisenatide, head-to-head data were not available and thus the data were taken from a network meta-analysis (NMA). Only significant treatment effects were included in the analysis. The CUA model assumed that the 52 week outcomes for HbA1c would apply in the first year and thereafter HbA1c was assumed to progress as per CORE progression (0.15% per year). For BMI changes, this was assumed to apply for the first year and thereafter when patients switch to insulin treatment (year 3 onwards) the BMI for both treatment groups immediately reverts to base line. The duration of GLP-1 agonist therapy was assumed to be for 2 years and thereafter patients were assumed to switch to insulin glargine.

Costs of microvascular and macrovascular complications in the CUA were taken from published studies. Utilities were also taken from published sources commonly used in diabetes models. The analysis took account of differential utility values according to some of the characteristics of treatments, for example, treatment frequency and injection site reactions. A gain of 0.023 for dulaglutide compared to daily treatments and a disutility of 0.011 for injection site reactions were assumed in the base case. The model also accounted for disutility associated with weight gain, as has been previously seen in other economic models.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dulaglutide	**1.5mg SC once weekly**	**952**
Liraglutide	1.2mg to 1.8mg SC once daily	952 to 1,428
Exenatide ER (Bydureon®)	2mg SC once weekly	954
Exenatide	5 to 10 micrograms SC twice daily	828
Lixisenatide	10 to 20 micrograms SC once daily	704

The results of the various comparisons are shown below:

[b] The IMS CORE Diabetes Model(IMS Health CDM) is accessible via the internet and simulates clinical outcomes and costs for cohorts of patients with diabetes. Drug therapies, lifestyle interventions, public health programs, medical devices and surgical interventions can all be modelled using the IMS Health CDM. It can be used for multiple purposes to estimate the impact of interventions on clinical and cost outcomes, as well as a range of economic analyses (cost-effectiveness, cost-utility, cost-benefit or cost of disease).

Dulaglutide versus:	Incremental cost	Incremental quality adjusted life year (QALY) where relevant	Incremental cost-effectiveness ratio (ICER) or CMA result
Liraglutide 1.2mg	-£29	n/a CMA	Dulaglutide is cost-minimising
Liraglutide 1.8mg	-£507	n/a CMA	Dulaglutide is cost-minimising
Liraglutide average daily dose	-£291	n/a CMA	Dulaglutide is cost-minimising
Exenatide ER	-£1	n/a CMA	Dulaglutide is cost-minimising
Lixisenatide	-£216	0.129	Dulaglutide is dominant (cheaper, more effective)
Exenatide twice daily	-£555	0.135	Dulaglutide is dominant

The results indicated that dulaglutide would be considered cost-effective against all comparators either on the basis of a dominant ICER versus lixisenatide and exenatide twice daily in the CUA or similar or lower price in the CMA versus liraglutide and exenatide ER. The CUA results versus lixisenatide and exenatide twice daily remained dominant in sensitivity analysis except when a treatment duration of 5 years or a 10 year model time horizon were assumed. In these cases, the ICERs were £1,057 and £996 respectively.[19]

Prescribing and risk management issues:

The licensed indications for albiglutide and dulaglutide are much wider than the relatively restrictive settings outlined in NICE guideline 28.[2,3,1] Approval of additional GLP-1 drugs should be supported with a re-iteration of the NICE guideline to ensure patients are treated only in NICE supported indications.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Albiglutide	30mg or 50mg once weekly	£71.00 for 4 injections	£923.00
Dulaglutide	0.75 or 1.5mg once weekly	£73.25 for 4 injections	£953.25
Exenatide ER	2 mg once weekly	£73.36 for 4 injections	£953.68
Exenatide	5µg to 10 µg twice daily	£68.24 for 30 day's injections	£818.88
Liraglutide	1.2mg to 1.8mg once daily	£78.48 - £117.72 for 30 day's injections	£941.76-£1412.64
Lixisenatide	20µg once daily	£57.93 for 30 day's injections	£695.16
Costs based on MIMS list prices May 2016. Table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

Patients will need to be taught how to use the injections and there will need to be arrangements for the safe disposal of sharps. The NICE Clinical Guideline on the treatment of type 2 diabetes in adults mandates specialist team input if GLP-1 drugs are to be used alongside insulin, stating:

- Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[1]

Anticipated patient numbers and net budget impact:

In their reviews, the SMC provided estimated uptake figures for both albiglutide and dulaglutide in years 1 and 5 with potential savings figures for each drug.[11,19]

Approximate equivalent figures for Lancashire have been calculated and are presented in the table, below:

	Year 1			Year 5		
	Patients treated	Drug Spend	Saving	Patients treated	Drug Spend	Saving
Albiglutide	159	£146,757	£283	204	£188,292	£3,116
Dulaglutide	67	£63,868	£12,181	550	£524,288	£67,138

Approximate figures per 100,000 population are presented in the table, below:

	Year 1			Year 5		
	Patients treated	Drug Spend	Saving	Patients treated	Drug Spend	Saving
Albiglutide	11	£9,784	£19	14	£12,553	£208
Dulaglutide	4	£4,258	£812	37	£34,952	£4,476

The NICE evidence review of dulaglutide calculates a slightly different figure that the SMC, estimating that 54 patients will be treated with dulaglutide in year 1, equivalent to 4 per 100,000 population; NICE did not provide a year 5 estimate.[20]

The All Wales Medicines Strategy Group have produced as preliminary Secretariat Report for dulaglutide.[27] The figures are therefore in draft form and with that caveat, the estimated patient uptake for Lancashire's is calculated to be 123 in year 1, rising to 777 in year 5. The figures per 100,000 population are 8 patients in year 1, rising to 52 patients in year 5.

Prescribing of GLP-1 Agonists in Lancashire: Financial year 2015/16

Drug	Quantity x items	Cost	Cost per year	Calculated patients
Albiglutide 30mg/0.5ml once weekly	0	£0	£923.00	0
Albiglutide 50mg/0.5ml once weekly	0	£0	£923.00	0
Dulaglutide 0.75mg/0.5ml once weekly (monotherapy)	55	£3,838	£953.25	4
Dulaglutide 1.5mg/0.5ml once weekly (add-on therapy)	513	£38,351	£953.25	40
Exenatide once weekly 4 pack	5,276	£343,997	£953.68	361

Exenatide twice daily 60 dose pack	4,442	£342,213	£818.88	418
Liraglutide once daily 3ml pre-filled pen	15,984	£1,403,047	£941.76-£1412.64	993-1,490
Lixisenatide once daily 20µg	1,333	£78,056	£695.16	112
Prescribing figures sourced using ePACT.net. Costs based on MIMS list prices May 2016. Table does not imply therapeutic equivalence of drugs or doses.				

Innovation, need, equity:

Albiglutide and dulaglutide are the fourth and fifth GLP-1 agonists to be licensed in the UK for the treatment of diabetes and the second/third in a once-weekly formulation (after exenatide extended release [ER]). There are therefore now a range of options for treating patients with a once daily preparation, giving scope to try alternatives if exenatide extended release is not tolerated or not suitable for a patient.

Head to Head Comparison of Effects of GLP-1 agonists

NICE Guideline 28 outlines the situations in which GLP-1 agonists may be prescribed and also defines the positive metabolic response that must be demonstrated for continued prescribing of a GLP-1 agonist, as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and**
- a weight loss of at least 3% of initial body weight in 6 months[1]

The phase III clinical programs for exenatide twice daily, exenatide once weekly, liraglutide, albiglutide, lixisenatide, and dulaglutide, have been reviewed to evaluated the safety and efficacy of GLP-1 agonist active comparators.[28,29,30] The results of these analyses provide an indication of the likelihood of NICE criteria for drug continuation being met.

In addition to the studies already covered for albiglutide and dulaglutide in the main sections of the New Medicine Review, the following studies demonstrate the effect of various GLP-1 agonists on HbA1c and body weight in trial subjects:

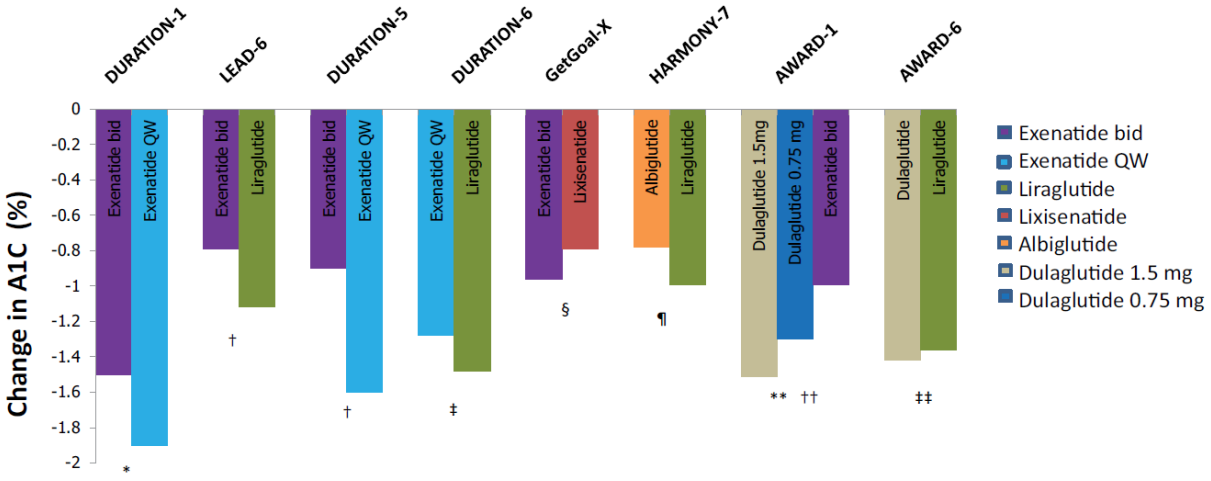
- The DURATION-1 study compared exenatide once weekly with exenatide twice daily in patients with uncontrolled type 2 diabetes being treated with either diet, one or two oral therapies.[31] After 30 weeks, exenatide once weekly reduced HbA1c significantly more compared with the twice daily formulation (–1.9% versus –1.5%; 95% CI –0.54% to –0.12%, p = 0.0023). Body weight decreased similarly between the two groups throughout the 30-week study with a –3.7 and –3.6 kg reduction from baseline in the exenatide weekly and twice daily groups, respectively (p = 0.89)
- An extension study of DURATION-1 to 52 weeks was conducted.[32] The extension study converted the exenatide twice daily patients to the weekly formulation for an additional 22 weeks, while those originally randomized to exenatide once weekly continued this during the follow up period. After 52 weeks patients continued on the once weekly exenatide maintained an HbA1c improvement (–2.0%) while those switching from twice daily to once weekly further reduced HbA1c to achieve a similar reduction in HbA1c as those originally on exenatide once weekly.
- In the LEAD-6 trial[33] patients on maximally tolerated doses of metformin, sulfonylurea or both were randomized to liraglutide or exenatide twice daily. Liraglutide reduced HbA1c significantly more than exenatide twice daily (–1.12% versus –0.79%; 95% CI –0.47 to –0.18, p < 0.0001). The percentage of subjects achieving weight loss (liraglutide 78% versus exenatide 76%) and overall weight loss (liraglutide –3.24 kg versus exenatide 2.87 kg, p = 0.22) was similar between groups.
- The DURATION-5 study compared exenatide once weekly to exenatide twice daily.[34,35] After

24 weeks, a significant reduction in HbA1c was observed with once weekly compared with twice daily exenatide (–1.6 versus –0.9%, p < 0.0001). As with the DURATION-1 trial, exenatide once weekly significantly lowered fasting glucose when compared with the twice daily formulation (–1.9 versus –0.7 mmol/l, p = 0.0008). A similar reduction in body weight was observed between groups.

- In the DURATION-6[18] trial, exenatide once weekly was compared to liraglutide. Reductions in HbA1c from baseline were significantly greater in patients taking liraglutide compared with exenatide once weekly (–1.48 versus –1.28%, p = 0.02). This difference of 0.21% did not meet predefined noninferiority criteria (95% CI 0.08–0.33). Patients in the liraglutide group lost 0.9 kg more body weight compared with exenatide once weekly (–3.57 versus –2.68, p = 0.0005). Both liraglutide and exenatide significantly reduced fasting blood glucose from baseline (–2.12 versus –1.76 mmol/l, p = 0.02).
- The GetGoal-X trial compared the efficacy and safety of lixisenatide to exenatide twice daily in patients with uncontrolled T2D on metformin.[36] The mean change in HbA1c was –0.79% in the lixisenatide group compared with –0.96% in the exenatide twice daily group. Body weight was significantly reduced in both groups, although a greater reduction was seen with exenatide (lixisenatide –2.96 kg versus exenatide –3.98 kg; 95% CI 0.45–1.58).

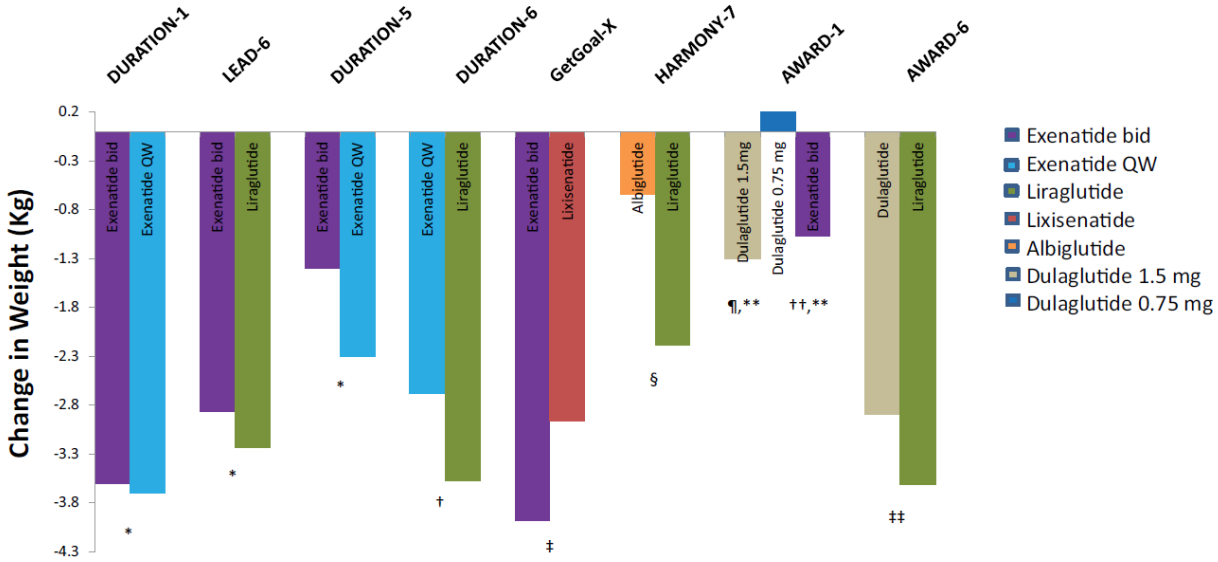
The results of the studies included in the analyses are presented in the two figures, below.

Figure 1: Reductions in HbA1c in phase III randomized head-to-head studies of GLP-1 agonists in type 2 diabetes.[28]



p-values are for statistical superiority unless otherwise noted as noninferiority; *p < 0.0025, †p < 0.0001, ‡p = 0.02, §p = not significant, noninferiority p-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority p-value = 0.846 (not meeting predefined noninferiority margin), **p < 0.001 for both doses of dulaglutide versus exenatide bid, ††p = not significant, noninferiority p-value < 0.0001 (meeting predefined noninferiority margin).

Figure 2: Changes in weight in published phase III randomized head-to-head studies of GLP-1 agonists in type 2 diabetes[28]



p-values are for statistical superiority (unless noted for noninferiority); *p = not significant, †p = 0.0005, ‡p-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §p < 0.0001, ¶ p < 0.001 versus dulaglutide 0.75 mg, **p = not significant between dulaglutide 1.5 mg versus exenatide bid, ‡‡p = 0.011

The major adverse events seen with the head-to-head GLP-1 agonists trials are summarised in the tables, below. Most of the adverse events experienced were GI in nature. Hypoglycemia rates were similar across GLP-1 agonists and were primarily seen in patients treated with a concomitant sulfonylurea. Across trials, however, there were some differences highlighted between comparators with regards to reported adverse events, as illustrated in the table, below.

GLP-1 agonists: a comparison of common adverse effects in head-to-head trials

Study	Active comparators	Nausea	Vomiting	Diarrhea	Injection-site reactions	Withdrawal due to AEs (*N*)
DURATION-1 [Drucker *et al.* 2008]	Exenatide 10 µg BID	50/145 (34.5%)	27/145 (18.6%)	19/145 (13.1%)	17/145 (11.7%)	7
	Exenatide 2 mg QW	39/148 (26.4%)	16/148 (10.8%)	20/148 (13.5%)	33/148 (22.3%)	9
LEAD-6 [Buse *et al.* 2009]	Exenatide 10 µg BID	65/232 (28.0%)	23/232 (9.9%)	28/232 (12.1%)	21/232 (9.1%)	31
	Liraglutide 1.8 mg QD	60/235 (25.5%)	14/235 (6.0%)	29/235 (12.3%)	21/235 (8.9%)	23
DURATION-5 [Blevins *et al.* 2011]	Exenatide 10 µg BID	43/123 (35.0%)	11/123 (8.9%)	5/123 (4.1%)	16/123 (13%)	6
	Exenatide 2 mg QW	18/129 (14.0%)	6/129 (4.7%)	12/129 (9.3%)	13/129 (10%)	6
DURATION-6 [Buse *et al.* 2013]	Exenatide 2 mg QW	43/461 (9.3%)	17/461 (3.7%)	28/461 (6.1%)	73/461 (15.8%)	12
	Liraglutide 1.8 mg QD	93/450 (20.7%)	48/450 (10.7%)	59/450 (13.1%)	9/450 (2.0%)	25
GetGoal-X [Rosenstock *et al.* 2013]	Lixisenatide 20 µg QD	78/318 (24.5%)	32/318 (10.1%)	33/318 (10.4%)	27/318 (8.5%)	33
	Exenatide 10 µg BID	111/316 (35.1%)	42/316 (13.3%)	42/316 (13.3%)	5/316 (1.6%)	41
HARMONY-7 [Pratley *et al.* 2014]	Albiglutide 50 mg QW	40/404 (9.9%)	20/404 (5.0%)	60/404 (14.9%)	52/404 (12.9%)	31
	Liraglutide 1.8 mg QD	119/408 (29.2%)	38/408 (9.3%)	55/408 (13.5%)	22/408 (5.4%)	41
AWARD-1 [Wysham *et al.* 2014]	Dulaglutide 1.5 mg QW	78/279 (28.0%)	47/279 (16.8%)	31/279 (11.1%)	1/279 (0.4%)	8
	Dulaglutide 0.75 mg QW	45/280 (16.1%)	17/280 (6.1%)	22/280 (7.9%)	0/280 (0%)	4
	Exenatide 10 µg BID	71/276 (25.7%)	30/276 (10.9%)	16/276 (5.8%)	1/276 (0.4%)	9
	Placebo					
AWARD-6 [Dungan *et al.* 2014]	Dulaglutide 1.5 mg QW	61/299 (20.4%)	21/299 (7.0%)	36/299 (12.0%)	1/299 (0.3%)	18
	Liraglutide 1.8 mg QD	54/300 (18.0%)	25/300 (8.3%)	36/300 (12.0%)	2/300 (0.7%)	18

Abbreviations: BID, twice daily; QD, once daily; QW, once weekly; AE, adverse event.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] NICE Guideline 28 - Type 2 diabetes in adults: management, 2 December 2015 https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-1837338615493 [accessed online on 9 May 2016].

[2] Electronic Medicines Compendium, Summary of Product Characteristics for Eperzan ® (Albiglutide) https://www.medicines.org.uk/emc/medicine/31400 [accessed online on 9 May 2016]

[3] Electronic Medicines Compendium, Summary of Product Characteristics for Trulicity® (Dulaglutide) https://www.medicines.org.uk/emc/medicine/29747 [accessed online on 9 May 2016]

[4] British Medical Association and the Royal Pharmaceutical Society, British National Formulary https://www.medicinescomplete.com/mc/bnflegacy/current/PHP4173-other-antidiabetic-drugs.htm [accessed online on 9 May 2016]. Albiglutide and Dulaglutide are not yet listed in the BNF, which was last updated in April 2016. There is already a section for the existing GLP1-agonists.

[5] Haymarket Media Group, eMIMS online http://www.mims.co.uk/drugs/diabetes/oral-and-parenteral-hypoglycaemics/eperzan [accessed online on 9 May 2016].

[6] Haymarket Media Group, eMIMS online http://www.mims.co.uk/drugs/diabetes/oral-and-parenteral-hypoglycaemics/trulicity [accessed online on 9 May 2016].

[7] NICE TA315: Canagliflozin in combination therapy for treating type 2 diabetes. 25 June 2014. https://www.nice.org.uk/guidance/ta315/resources/canagliflozin-in-combination-therapy-for-treating-type2-diabetes-82602428123077 [accessed online on 10 May 2016]

[8] NICE TA288: Dapagliflozin in combination therapy for treating type 2 diabetes. 26 June 2013. https://www.nice.org.uk/guidance/ta288/resources/dapagliflozin-in-combination-therapy-for-treating-type2-diabetes-82600679642821 [accessed online on 10 May 2016]

[9] NICE TA336: Empagliflozin in combination therapy for treating type 2 diabetes. 25 March 2015. https://www.nice.org.uk/guidance/ta336/resources/empagliflozin-in-combination-therapy-for-treating-type2diabetes-82602550735045 [accessed online on 10 May 2016]

[10] LMMG web site: Lixisenatide. 11 July 2013. http://www.lancsmmg.nhs.uk/wp-content/uploads/sites/3/2013/07/LIXISENATIDE-LMMG-New-Medicine-Review-Form-Final-Recommendation-following-LMMG-Website.pdf [accessed online on 10 May 2016]

[11] Scottish Medicines Consortium: Albiglutide review https://www.scottishmedicines.org.uk/files/advice/albiglutide_Eperzan_FINAL_Jan_2015_Issued_Dec_2015_amended_031215_for_website.pdf [accessed online on 10 May 2016]

[12] Basildon and Thurrock University Hospitals, HbA1c Conversion Table (Glycaemic Control) table, available online http://baspath.co.uk/Hba1c_table.pdf [accessed on 26 May 2016]

[13] Ahern B, Johnson SL, Stewart M et al. HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin. Diabetes Care 2014; 37: 2141-8

[14] Prately RE, Nauck MA, Barnett AH et al. Once weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY-7): a randomised, open-label, multicentre, noninferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289-97

[15] Rosenstock J, Fonseca VA, Gross JL et al. Advancing Basal Insulin Replacement in Type 2 Diabetes Inadequately Controlled With Insulin Glargine Plus Oral Agents: A Comparison of Adding Albiglutide, a Weekly GLP-1 Receptor Agonist, Versus Thrice-Daily Prandial Insulin Lispro. Diabetes Care 2014; 37: 2317–25

[16] EPAR Eperzan ® http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002735/WC500165119.pdf [accessed online on 10 May 2016]

[17] Prately RE, Nauck MA, Barnett AH et al. Once weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY-7): a randomised, open-label, multicentre, noninferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289-97

[18] Buse JB, Nauck M, Forst T et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381: 117-24

[19] Scottish Medicines Consortium: Dulaglutide review https://www.scottishmedicines.org.uk/files/advice/dulaglutide_Trulicity_FINAL_December_2015_amended_040116_for_website.pdf [accessed online on 10 May 2016]

[20] NICE Evidence summary: new medicine. Type 2 diabetes: dulaglutide, 15 June 2015 https://www.nice.org.uk/guidance/esnm59/resources/type-2-diabetes-dulaglutide-1502681053154245 [accessed online on 11 May 2016]

[21] Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014; 37(8): 2159-67

[22] Giorgino F, Benroubi M, Sun JH, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Available online ahead of publication in Diabetes Care 2015; June 18, 2015, doi: 10.2337/dc14-1625.

[23] EPAR Trulicity http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002825/WC500179473.pdf [accessed online on 11 May 2016]

[24] Reaney M, Yu M, Lakshmanan M, et al. Treatment satisfaction in people with type 2 diabetes mellitus treated with once-weekly dulaglutide: data from the AWARD-1 and AWARD-3 clinical trials. Diabetes Obesity and Metabolism 2015; 17: 896-903.

[25] Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014; 384(9951): 1349-57.

[26] IMS Core diabetes model http://www.core-diabetes.com/about-the-cdm.html [accessed online on 11 May 2016]

[27] All Wales Medicines Strategy Group Secretariat Assessment Report Ref: 866 Dulaglutide (Trulicity®) 1.5 mg and 0.75 mg solution for injection http://www.awmsg.org/awmsgonline/grabber?resId=2197 [accessed online on 12 May 2016]

[28] Trujillo J, Nuffer W and Ellis S. GLP-1 receptor agonists: a review of head to head clinical studies, Ther Adv Endocrinol Metab, 2015, Vol. 6(1) 19–28

[29] Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012; 344: d7771.

[30] Niswender K, Pi-Sunyer X, Buse J et al. Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. Diabetes Obes Metab 2013; 15: 42–54.

[31] Drucker DJ, Buse JB, Taylor K et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008; 372: 1240–1250

[32] Buse, J., Drucker, D., Taylor, K., Kim, T., Walsh, B., Hu, H. et al. (2010) DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care 33: 1255–1261.

[33] Buse JB, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374: 39–47.

[34] Ji L, Onishi Y, Ahn CW et al. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. J Diabetes Invest 2013; 4: 53–61

[35] Blevins T, Pullman J, Malloy J et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96: 1301–1310.

[36] Rosenstock J, Raccah D, Korányi L et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013; 36: 2945–2951.