Dulaglutide: a once-weekly GLP-1 for type 2 diabetes

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Dulaglutide is a once-weekly GLP-1 receptor agonist for the treatment of type 2 diabetes. Steve Chaplin presents the clinical data relating to its efficacy and adverse events and Professor Stephen Bain discusses its place in therapy.

KEY POINTS

- Dulaglutide (Trulicity) is a once-weekly GLP-1 receptor agonist for the treatment of type 2 diabetes
- As monotherapy, it is at least as effective as metformin in lowering HbA1c
- As second- or third-line therapy, it reduces HbA1c significantly more than sitagliptin, insulin glargine and twice-daily exenatide and is non-inferior to lixisenatide
- Weight loss with dulaglutide is similar to twice-daily exenatide, less than with lixisenatide but more than with other comparators
- Adverse effects are typical of a GLP-1 receptor agonist, the most common being nausea in the first two weeks
- A year’s treatment with dulaglutide 1.5mg weekly costs £1182

Steve Chaplin

Draft NICE guidance on the management of type 2 diabetes recommends a GLP-1 receptor agonist (RA), in combination with metformin and sulfonylurea, as fourth-line therapy as an alternative to three oral glucose-lowering drugs or introducing insulin.1

This should be considered for patients with: a BMI of ≥35kg/m² and specific psychological or other medical problems associated with obesity; or those with a lower BMI when insulin therapy would have significant occupational implications or when weight loss would benefit other significant obesity-related co-morbidities.

The choice of GLP-1 RA should reflect patient preference, then cost. Treatment should be discontinued if, after six months, HbA1c has not fallen by at least 1 per cent and weight loss is at least 3 per cent of baseline. A GLP-1 RA should be combined with insulin only in a specialist setting, which may include a GP with a special interest in diabetes.

There are now four GLP-1 RAs to choose from: twice-daily (Byetta) or weekly (Bydureon) exenatide, daily liraglutide (Victoza) or lixisenatide (Lyxumia), and weekly dulaglutide (Trulicity; albiglutide also has a European licence but has not yet been launched in the UK). Weekly exenatide (Bydureon) is a short-acting GLP-1 RA that is formulated in prolonged-release microspheres. Dulaglutide comprises two GLP-1-like molecules covalently bound to an immunoglobulin fragment. It is slowly absorbed and resistant to degradation by the enzyme DPP-4; its half-life is 4.7 days.

Dulaglutide

Dulaglutide is a long-acting GLP-1 RA for administration by subcutaneous injection. It is licensed for the treatment of type 2 diabetes in adults when exercise and diet are not sufficient, as monotherapy when metformin is unsuitable, or in combination with other glucose-lowering drugs (including insulin). The recommended dose for monotherapy is 0.75mg once weekly; as add-on therapy, it is 1.5mg once weekly. The risk of hypoglycaemia is increased when dulaglutide is added to established treatment with mealtime insulin or a
sulfonylurea and a lower dose of these drugs should be considered (GLP-1 RAs do not cause hypoglycaemia on their own but there is an increased risk of hypoglycaemia from insulin or a sulfonylurea when combination therapy is used).

No dose adjustment is recommended for people over the age of 65 but the starting dose should be 0.75mg weekly for those aged over 75. There is no dose reduction for patients with hepatic impairment or mild or moderate renal impairment. There is little experience in patients with severe renal impairment or end stage renal disease and dulaglutide is not recommended for such individuals.

The dose can be administered at any time of day, regardless of meals. If a dose is missed, it should be administered as soon as possible up to 72 hours before the next scheduled dose. If that dose is due within 72 hours, the missed dose should be skipped and the next dose administered as scheduled and the normal weekly regimen resumed. The day of injection can be changed provided the last dose was administered at least 72 hours previously.

No clinically significant drug interactions are known. As with other GLP-1 agonists, dulaglutide should be discontinued if pancreatitis is suspected; patients should be informed of the symptoms of acute pancreatitis.

**Clinical trials**
Dulaglutide was evaluated as monotherapy and in combination with other glucose-lowering drugs in the AWARD trial programme, involving a total of 5171 patients.²⁻⁷

**Monotherapy**
In patients with baseline HbA₁c of about 7.6 per cent, dulaglutide 0.75mg weekly reduced HbA₁c significantly more than metformin 1.5–2.0mg/day after six months (by 0.71 vs 0.61 per cent; p<0.025) and one year (0.55 vs 0.39 per cent; p<0.001–0.025). The proportions of patients with HbA₁c <7.0 per cent were 61, 58 and 54 per cent at each timepoint, and significantly greater than with sitagliptin (38, 33 and 31 per cent; all p<0.001). The corresponding figures for weight loss were 3.18, 3.03 and 2.88kg for dulaglutide and 1.46, 1.53 and 1.75kg for sitagliptin (all p<0.001).³

Dulaglutide 1.5mg/week was non-inferior to liraglutide 1.8mg/day after 26 weeks’ treatment, with a mean reduction in HbA₁c of 1.42 vs 1.36 per cent. HbA₁c was <7.0 per cent in about 68 per cent of patients in each group. Liraglutide was associated with significantly greater weight loss (3.6kg vs 2.9kg, p<0.05).⁷

**Combination with metformin**
As add-on therapy in patients with HbA₁c of about 8.1 per cent despite treatment with metformin, dulaglutide has been compared with sitagliptin (Januvia)³ and liarglutide.⁷

Dulaglutide 1.5mg weekly reduced HbA₁c by significantly more than sitagliptin 100mg/day at 26 weeks (1.22 vs 0.61 per cent; one year (1.10 vs 0.39 per cent) and two years (0.99 vs 0.32 per cent; p<0.001–0.025). The proportions of patients with HbA₁c <7.0 per cent were 61, 58 and 54 per cent at each timepoint, and significantly greater than with sitagliptin (38, 33 and 31 per cent; all p<0.001). The corresponding figures for weight loss were 3.18, 3.03 and 2.88kg for dulaglutide and 1.46, 1.53 and 1.75kg for sitagliptin (all p<0.001).³

**Triple combination therapy**
Dulaglutide has been compared with insulin glargine as add-on therapy to metformin/glimepiride³ and with twice-daily exenatide as add-on therapy to metformin/pioglitazone.²

In patients with baseline HbA₁c 8.1–8.2 per cent despite treatment with metformin/glimepiride, dulaglutide 1.5mg/ week improved glycaemic control significantly more than basal insulin glargine (dose adjusted to fasting plasma glucose, FPG <5.6mmol/L) at 56 weeks (HbA₁c reduced by 1.08 vs 0.63 per cent) and 72 weeks (0.90 vs 0.59 per cent; both p<0.025). Significantly more patients who had received dulaglutide had HbA₁c <7.0 per cent at these times (53 vs 31 per cent and 49 vs 31 per cent respectively; both p<0.001). Insulin was associated with weight gain (1.28kg at 72 weeks) whereas dulaglutide resulted in weight loss (1.96 kg).³

Patients with HbA₁c 8.1 per cent despite treatment with metformin/pioglitazone were randomised to dulaglutide or exenatide 5µg twice daily for four weeks then 10µg twice daily. Dulaglutide 1.5mg/week improved glycaemic control by significantly more than exenatide after 26 weeks (HbA₁c reduced by 1.51 vs 0.99 per cent) and 52 weeks (1.36 vs 0.80 per cent; both p<0.025; see Figure 1). The proportions of patients with HbA₁c <7.0 per cent were 78 and 71 per cent with...
Dulaglutide and 52 and 49 per cent with exenatide (p<0.001). Weight loss was not significantly different (1.30 vs 1.1kg and 1.1 vs 0.8kg at 26 and 52 weeks). 2

**Combination with mealtime insulin**

Dulaglutide was compared with basal insulin glargine (target FPG <5.6mmol/L) as add-on therapy to mealtime insulin lispro (Humalog), with or without metformin in patients with HbA1c 8.4–8.5 per cent. After 26 weeks, HbA1c was reduced by 1.64 per cent with dulaglutide 1.5mg/week and 1.41 per cent with insulin glargine; at 52 weeks, the figures were 1.48 and 1.23 per cent (both p<0.025 for dulaglutide vs insulin glargine). More patients treated with dulaglutide achieved HbA1c <7.0 per cent (68 vs 57 per cent and 58 vs 49 per cent; p<0.05). Insulin glargine was associated with weight gain (2.9kg after 52 weeks) whereas dulaglutide caused weight loss (0.9kg).

**Adverse effects**

In clinical trials, the adverse events associated with dulaglutide were typical of GLP-1 RAs and more common with the 1.5mg dose. 8 The most frequent events were nausea (21 per cent, largely in the first two weeks), diarrhoea (14 per cent) and vomiting (12 per cent). Adverse gastrointestinal events caused early treatment discontinuation in 4.8 per cent of patients receiving the higher dose.

**References**


**Declaration of interests**

None to declare.

Steve Chaplin is a pharmacist who specialise in writing on therapeutics

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**Place in therapy**

**Stephen Bain**

Once-weekly glucose medications have been available in the UK since the launch of exenatide as Bydureon in 2011; however, this has not been the “game-changer” that many predicted. There are several reasons for this, the first being that the efficacy of once-weekly exenatide was not as impressive as had originally been anticipated.

In the DURATION 1 study, exenatide 2mg once-weekly achieved an HbA1c reduction of 2 per cent at six months, the best seen for any new add-on medication. However, when a new factory formulation was trialled in a similar manor in EDITION 5, the HbA1c was a less impressive 1.6 per cent fall. This may have led to over-optimistic goals for the DURATION 6 study where, in a head-to-head with 1.8mg liraglutide, once-weekly exenatide was shown to be “inferior”.

The weekly administration has also been problematic, since once-weekly exenatide is a subcutaneous injection of a microsphere suspension. This powder needs to be thoroughly mixed using a syringe and vial in a procedure so complex that patients were directed to an online video.

The large needle size (23 gauge) was also an issue, along with injection-site nodules, which typically take four weeks to dissipate (as the microspheres are slowly absorbed). Some of these problems have now been resolved with the introduction of a new injection device, launched in 2014.

Once-weekly exenatide was also at the centre of various company fallouts and take-over. This has led to disjointed and low-key marketing.

Dulaglutide (Trulicity) will overcome most of these problems. It comes to market with the full backing of its parent company, has a really simple-to-use device and is the first GLP-1 RA to be shown to be non-inferior to liraglutide (at least in terms of HbA1c reduction).

It has the anticipated tolerability profile of a GLP-1 RA and will appeal to patients who do not like daily injecting. It will also be time-saving where healthcare professionals currently have to administer the GLP-1 therapy.

One outstanding issue will be cost; although dulaglutide is less expensive than liraglutide 1.8mg once daily, it is more costly than liraglutide 1.2mg once daily, the dose currently sanctioned by NICE guidelines.

**Declaration of interests**

Professor Bain has received grants and honoraria from Eli Lilly, Novo Nordisk and Sanofi.

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