NEW DRUGS

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Dulaglutide

Approved indication: type 2 diabetes
Trulicity (Eli Lilly)
pre-filled pens and syringes containing 1.5 mg/0.5 mL solution
Australian Medicines Handbook section 10.1.4

When drug treatment is needed for type 2 diabetes, patients are usually prescribed metformin. If this does not control blood glucose, a second drug may need to be added.[1] This includes the glucagon-like peptide-1 (GLP-1) analogues, such as exenatide and liraglutide. Like these drugs, dulaglutide acts as an agonist at the GLP-1 receptor. It therefore increases the secretion of insulin when glucose concentrations are high.

Dulaglutide is a genetically engineered protein. It therefore has to be given by subcutaneous injection. The way the molecule is engineered slows its absorption and clearance. Peak plasma concentrations are reached in 48 hours and the half-life is 4.7 days. This makes dulaglutide suitable for once-a-week injections. It takes 2–4 weeks to reach a steady state. The molecule is catabolised and no dose adjustment is required for hepatic impairment or mild–moderate kidney impairment.

There have been multiple studies of dulaglutide as monotherapy and in combination with other drugs. Its approval in Australia is based on five main trials (Table).[2-6] Although the recommended weekly dose is 1.5 mg, these AWARD trials also studied 0.75 mg.

Monotherapy

Dulaglutide was compared with metformin in a double-blind trial involving 807 patients with type 2 diabetes of less than five years duration. At the start of the AWARD-3 study the mean concentration of glycated haemoglobin (HbA1c) was 59.6 mmol/mol (7.6%). After 26 weeks this had reduced by 8.5 mmol/mol (0.78%) with dulaglutide 1.5 mg and by 6.1 mmol/mol (0.56%) with metformin. A target HbA1c concentration below 53 mmol/mol (7%) was achieved by 62% of the patients taking dulaglutide and 54% of those taking metformin. These statistically significant advantages for dulaglutide 1.5 mg were still present after 52 weeks of treatment.[2]

Added to metformin

In the AWARD-5 trial, 1098 patients treated with metformin were randomised to add dulaglutide, sitagliptin 100 mg daily or placebo. After 26 weeks the patients taking placebo changed to sitagliptin. At the start of the study the mean HbA1c was 65 mmol/mol (8.1%). After 26 weeks this reduced by 13.3 mmol/mol (1.22%) with dulaglutide 1.5 mg, 6.7 mmol/mol (0.61%) with sitagliptin and 0.3 mmol/mol (0.03%) with placebo. The reductions from baseline at 52 weeks were 12 mmol/mol (1.1%) for dulaglutide and 4.3 mmol/mol (0.39%) for sitagliptin. Dulaglutide therefore had a significant advantage over sitagliptin. A target concentration under 53 mmol/mol (7%) was achieved by 58% of patients injecting dulaglutide and 33% of those taking sitagliptin.[3]

Table **Pivotal efficacy trials of dulaglutide in type 2 diabetes**

Trial (comparator)	Total number of patients (number treated with dulaglutide 1.5 mg weekly)	Total duration	Time of primary endpoint assessment	Reduction in HbA1c from baseline in mmol/mol (%) at primary end point		Proportion of patients achieving an HbA1c below 53 mmol/mol (7%) at primary end point
AWARD-1[4] (exenatide)	976 (279)	52 weeks	26 weeks	Dulaglutide	16.5 (1.51%)	78%
				Exenatide	10.8 (0.99%)	52%
AWARD-2[5] (insulin glargine)	810 (273)	78 weeks	52 weeks	Dulaglutide	11.8 (1.08%)	53.2%
				Insulin glargine	6.9 (0.63%)	30.9%
AWARD-3[2] (metformin)	807 (269)	52 weeks	26 weeks	Dulaglutide	8.5 (0.78%)	62%
				Metformin	6.1 (0.56%)	54%
AWARD-4[6] (insulin glargine)	884 (295)	52 weeks	26 weeks	Dulaglutide	17.9 (1.64%)	68%
				Insulin glargine	15.4 (1.41%)	57%
AWARD-5[3] (sitagliptin)	1098 (304)	104 weeks	52 weeks	Dulaglutide	12.0 (1.1%)	58%
				Sitagliptin	4.3 (0.39%)	33%

HbA1c glycated haemoglobin

Added to metformin and a thiazolidinedione

Patients in the AWARD-1 trial were stabilised on a combination of metformin and pioglitazone. The 976 patients were then randomised to have weekly injections of dulaglutide or exenatide. There was also a group of patients who injected a placebo for 26 weeks then switched to dulaglutide. From a mean baseline of 65 mmol/mol (8.1%), the HbA1c had fallen by 16.5 mmol/mol (1.51%) with dulaglutide 1.5 mg and by 10.8 mmol/mol (0.99%) with exenatide at 26 weeks. The reduction in the placebo group was 5 mmol/mol (0.46%). At 52 weeks the reduction from baseline was statistically significantly greater with dulaglutide than exenatide (14.9 vs 8.8 mmol/mol (1.36% vs 0.89%)). The goal of an HbA1c concentration below 48 mmol/mol (6.5%) was achieved by 57% of the dulaglutide group and 35% of the exenatide group.[4]

Added to metformin and a sulfonylurea

Dulaglutide has been compared to insulin when treatment with metformin and glimepiride has been insufficient to control type 2 diabetes. In the open-label AWARD-2 trial 810 patients with an average HbA1c of 65–66 mmol/mol (8.1–8.2%) were randomised to inject dulaglutide weekly or insulin glargine daily. After 52 weeks the HbA1c had reduced by 11.8 mmol/mol (1.08%) with dulaglutide 1.5 mg and 6.9 mmol/mol (0.63%) with insulin glargine. This gave dulaglutide a statistical advantage. There was also a significant difference in the proportion of patients who achieved a target HbA1c below 53 mmol/mol (7%) (53.2% dulaglutide, 30.9% insulin). The statistical superiority of dulaglutide 1.5 mg over insulin was still present after 78 weeks of treatment.[5]

Added to insulin

The open-label AWARD-4 trial involved 884 patients who were using insulin lispro with or without metformin. They were randomised to receive weekly dulaglutide or a bedtime injection of insulin glargine. From a baseline concentration of 68.95 mmol/mol (8.46%), HbA1c reduced by 17.93 mmol/mol (1.64%) after 26 weeks with dulaglutide 1.5 mg. With insulin glargine it reduced by 15.41 mmol/mol (1.41%) from a baseline of 69.72 mmol/mol (8.53%). This statistically significant difference was still present at 52 weeks. At that time, 59% of the patients injecting dulaglutide 1.5 mg had an HbA1c below 53 mmol/mol (7%) compared with 49% of those injecting insulin glargine.[6]

Safety

In studies lasting up to 104 weeks 8.4% of the patients injecting dulaglutide discontinued it because of adverse effects. Nausea, vomiting and diarrhoea are very common, particularly at the start of therapy. Pancreatitis is a possibility, but enzyme concentrations can be unhelpful for making the diagnosis as they rise during treatment with dulaglutide.

Hypoglycaemia can occur particularly in patients who are also taking insulin or a sulfonylurea. A meta-analysis of 12 trials of dulaglutide reported that with monotherapy 7.8% of patients developed hypoglycaemia compared with 10.6% of those in control groups.[7] In the study of patients taking metformin and glimepiride (AWARD-2), 55.3% of those given dulaglutide for 52 weeks developed hypoglycaemia compared with 69.1% of those who added insulin glargine. This difference was significant.[5]

The meta-analysis reported that dulaglutide reduced body weight less than metformin, but more than sitagliptin, exenatide and insulin glargine.[7] Across the studies the reduction from baseline was 0.35–2.88 kg.

Dulaglutide increases the heart rate and slightly lowers systolic blood pressure. It is also associated with atrioventricular block. The risk of cardiovascular events does not appear to differ from that of control treatments.

Some patients develop antibodies to dulaglutide. This does not appear to make them more prone to hypersensitivity reactions.

Place in therapy

As the clinical outcomes for some of the newer drugs for type 2 diabetes are not yet clear, the optimum combination is uncertain.[1] If a GLP-1 analogue is selected, there are few differences between them. Dulaglutide appears to have a greater effect on HbA1c than exenatide[4] and is non-inferior compared to liraglutide.[8] Although the absolute differences are small, dulaglutide appears to reduce weight more than exenatide,[4] but less than liraglutide.[8] As liraglutide is given daily, patients who want to minimise injections may prefer weekly dulaglutide.

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At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.