

## New drugs



Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

### Liraglutide

#### Approved indication: type 2 diabetes

#### Victoza (Novo Nordisk)

#### pre-filled multidose disposable pens containing 1.2 mg/3 mL and 1.8 mg/3 mL

#### Australian Medicines Handbook section 10.1

Glucose in the gut stimulates the release of incretins such as glucagon-like peptide-1 (GLP-1). Incretins are hormones which increase insulin secretion and can be beneficial in diabetes. Like exenatide, liraglutide is a long-acting GLP-1 mimetic produced by DNA recombinant technology. It mimics the action of GLP-1, but, unlike natural incretins, is not rapidly degraded by the enzyme dipeptidyl peptidase 4.

Liraglutide should be prescribed as an adjunct to diet and exercise. It is indicated as an add-on therapy for adults with type 2 diabetes who have insufficient glycaemic control despite maximally tolerated doses of their current drug regimen. Liraglutide can be added to monotherapy with metformin or a sulfonylurea or used as a third treatment in combination with metformin and a sulfonylurea.

The effectiveness of adding liraglutide to other oral hypoglycaemic drugs has been assessed in several randomised controlled trials.<sup>1-6</sup> These were mainly short-term studies (26 weeks) and the primary outcome was the change in mean HbA1c from baseline to the end of the trial.

In one of the open-label trials, 464 patients taking metformin, a sulfonylurea or both were randomised to add liraglutide (1.8 mg a day subcutaneously) or exenatide (10 microgram twice a day subcutaneously). At baseline, mean HbA1c concentrations were 8.1-8.2%. By the end of the trial, average HbA1c concentrations had reduced by 1.12% with liraglutide and 0.79% with exenatide.<sup>1</sup>

In another open-label trial of 665 people already taking metformin (mean baseline HbA1c of 8.5%), adding liraglutide 1.2 mg or 1.8 mg reduced mean HbA1c concentrations by 1.24% and 1.5%. This was compared to sitagliptin (100 mg orally) which reduced HbA1c by 0.9%.<sup>2</sup>

Liraglutide (1.2 or 1.8 mg) has also been compared to rosiglitazone (4 mg) as an add-on to glimepiride monotherapy in a placebo-controlled trial. At the end of the study, mean HbA1c concentrations had decreased by 1.1% with liraglutide (389 people) and 0.4% with rosiglitazone (182 people). HbA1c had

increased by 0.2% in patients who added placebo (74 people).<sup>3</sup> In a similarly designed trial, mean HbA1c concentrations were reduced by 1% when liraglutide (1.2 or 1.8 mg) or glimepiride were added to metformin.<sup>4</sup>

In another trial, the higher dose of liraglutide (1.8 mg) was comparable to insulin glargine (titrated dose) when added to combination therapy with metformin and glimepiride. Mean HbA1c concentrations were reduced by 1.33% with liraglutide, 1.09% with insulin and 0.24% with placebo.<sup>5</sup> Mean HbA1c concentrations were also reduced (1.5%) when liraglutide was added to the combination of metformin and rosiglitazone.<sup>6</sup>

In the trials, more people who added liraglutide achieved an HbA1c target of less than 7% than those adding the placebo or the active comparator. Adding liraglutide (1.8 mg) to therapy was also associated with weight loss, however reductions were quite modest ranging from 0.2 to 3.38 kg.<sup>1-6</sup>

The most common adverse effects seen after adding liraglutide to therapy were gastrointestinal. Nausea and diarrhoea occurred in more than 10% of people. Vomiting, constipation, abdominal pain and dyspepsia were also common (1-10%). These adverse events were more likely to occur at the beginning of treatment and usually resolved on continued treatment, however there were withdrawals because of nausea (2.8%) and vomiting (1.5%). Headache, nasopharyngitis and hypoglycaemia were also quite common. Injection-site reactions were experienced by approximately 2% of trial participants, but these reactions were generally mild. A few cases of pancreatitis have been reported during long-term trials (12 months) with liraglutide.

On average, 8.6% of people in the trials developed antibodies to the liraglutide peptide. This has so far not been associated with reduced efficacy.

Liraglutide should be taken once a day by subcutaneous injection in the abdomen, thigh or upper arm. After injection, absorption is slow, with maximum concentrations being reached after 8-12 hours. Its elimination half-life is approximately 13 hours.

Liraglutide should not be used in patients with hepatic impairment (mild-severe) or severe renal impairment (creatinine clearance below 30 mL/minute), including those with end-stage renal disease. There is limited experience in patients with moderate renal impairment and those with congestive heart failure. Liraglutide is not recommended in people with inflammatory bowel disease or diabetic

gastroparesis. The human GLP-1 receptor is expressed at low levels on thyroid cells, and adverse events such as elevated blood calcitonin, goitres and thyroid cancers have been reported, particularly in patients with a pre-existing thyroid condition. Liraglutide should not be taken during pregnancy and lactation. Liraglutide delays gastric emptying and may affect the absorption of oral drugs given at the same time. It is not known if it interacts with warfarin so more frequent warfarin monitoring is recommended at the start of liraglutide treatment.

Concomitant use of a sulfonylurea increased the risk of hypoglycaemia in the trials, with more than 10% of patients being affected. More frequent blood glucose monitoring and dose adjustment of the sulfonylurea may be needed. Liraglutide is not recommended with insulin.

Liraglutide reduced HbA1c concentrations when added to oral glycaemic drugs in people with inadequately controlled type 2 diabetes. In short-term trials, its efficacy was similar to adding glimepiride, but was better than adding exenatide, sitagliptin, rosiglitazone or insulin. It is important to remember that HbA1c is only a surrogate marker for efficacy and it is not known if liraglutide will improve the morbidity and mortality associated with type 2 diabetes.

**T** manufacturer provided the AusPAR

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The T-score (**T**) is explained in 'New drugs: T-score for transparency', *Aust Prescr* 2011;34:26-7.

- \* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA ([www.fda.gov](http://www.fda.gov)).
- † At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency ([www.ema.europa.eu](http://www.ema.europa.eu)).
- A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration ([www.tga.gov.au/industry/pm-auspar.htm](http://www.tga.gov.au/industry/pm-auspar.htm))