

# NEW DRUG EVALUATION

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## LIRAGLUTIDE ▼

**Liraglutide is a once daily glucagon like peptide-1 (GLP-1) analogue administered subcutaneously as part of either dual or triple therapy for the treatment of type 2 diabetes. In randomised trials liraglutide reduced HbA<sub>1c</sub> to a greater extent than placebo or various active comparators. Liraglutide was more effective than exenatide at reducing HbA<sub>1c</sub>, while weight loss was similar with both drugs. The most commonly reported adverse effects are nausea, diarrhoea and vomiting. When a GLP-1 analogue is recommended in NICE guidance CG87, liraglutide is a suitable but more costly alternative to exenatide. It may be appropriate for use in patients who cannot tolerate exenatide or are unable to adhere to a twice daily regimen.**

### What is it?

Liraglutide (Victoza<sup>®</sup>▼, Novo Nordisk Ltd) is a glucagon like peptide-1 (GLP-1) analogue licensed for treating adults with type 2 diabetes mellitus as a component of either:<sup>1</sup>

- a) dual therapy - combined with metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximum tolerated doses of either drug or
- b) triple therapy - combined with metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Liraglutide is administered as a once daily subcutaneous injection.<sup>1</sup> The starting dose is 0.6 mg daily, increased to 1.2 mg after at least one week. If required the dose can be increased to 1.8 mg to further improve glycaemic control.<sup>1</sup> Liraglutide is a possible alternative to exenatide, but has the advantage of once daily dosing, irrespective of meals, compared with twice daily dosing for exenatide which has to be taken in relation to meals.<sup>2</sup> Liraglutide has a slightly broader indication than exenatide, which is only licensed in combination with metformin and/or a sulphonylurea.<sup>2</sup> The Company's marketing claims liraglutide provides additional beneficial characteristics to exenatide such as improved HbA<sub>1c</sub> and reductions in weight.<sup>3</sup>

### How effective is it?

The efficacy and safety of liraglutide in type 2 diabetic patients was assessed in the LEAD [Liraglutide Effect and Action in Diabetes] programme, a series of six randomised, parallel-group, multi-centre trials (n = 4,456), in which the therapeutic response to liraglutide (0.6 mg to 1.8mg) was compared with that of placebo and/or a specific comparator drug in varying combinations.<sup>4-9</sup> Active comparators included rosiglitazone, glimepiride, insulin glargine or exenatide. Five of the six trials combined liraglutide as dual therapy (with glimepiride, metformin or another sulphonylurea) or triple therapy (with metformin & rosiglitazone, metformin & glimepiride or metformin & another sulphonylurea). It should be noted that the dose of

the active comparator rosiglitazone (4 mg/day) in the dual therapy trial was lower than might have been expected in normal clinical use, and therefore is not the most appropriate of comparisons.

The studies, ranged from 26 to 52 weeks in duration with a primary endpoint of change in HbA<sub>1c</sub> from baseline to the end of the study.<sup>4-9</sup> The change in HbA<sub>1c</sub> across the six studies for the licensed dose of liraglutide (1.2 mg and 1.8 mg) ranged from a mean decrease of -0.8% to -1.5%. Active comparator changes ranged from a decrease of -1.1% (insulin glargine) to -0.4% (rosiglitazone). Placebo changes ranged from a decrease of -0.5% to an increase of +0.2%. Weight gain/loss with liraglutide, the latter an important marketing strategy, ranged from a loss of -3.2kg (1.8 mg) to a gain of +0.3kg (1.2 mg). Active comparator changes ranged from a loss of -2.9kg (exenatide) to a gain of +2.1kg (rosiglitazone). Placebo changes ranged from a loss of -1.5kg to a gain of +0.6kg

The LEAD 6<sup>9</sup> study (n = 464) compared liraglutide 1.8mg once daily with exenatide 10 mcg twice daily in combination with metformin, a sulphonylurea or both. HbA<sub>1c</sub> decreased significantly more with liraglutide than exenatide (-1.12% vs -0.79%, estimated treatment difference -0.33; 95% confidence interval (CI) -0.47 to -0.18, p < 0.0001). Weight loss was similar with both drugs (-3.24kg with liraglutide vs -2.87kg with exenatide, estimated treatment difference -0.38kg; 95% CI -0.99 to 0.23, p = 0.22).<sup>9</sup>

### How safe is it?

The most common adverse effects (AE) seen in the above studies were gastrointestinal (GI) e.g. nausea, diarrhoea and vomiting.<sup>4-10</sup> Rates of withdrawal due to these AEs were higher in the liraglutide groups than either the active comparator or placebo groups.<sup>10</sup> Overall GI AE rates ranged from 35 – 56% with liraglutide compared with 17 - 19% with placebo.<sup>4-9</sup>

A small number of cases of pancreatitis were reported in some of the trials, although it is unknown whether they were linked to liraglutide treatment.<sup>4,5,9</sup> The rates appear similar to the general type 2 diabetes population<sup>10</sup> but

patients taking liraglutide should be informed of the characteristic symptoms of acute pancreatitis (persistent, severe abdominal pain), and advised to seek medical advice if pancreatitis is suspected.<sup>1</sup> Thyroid adverse events have also been reported in patients with and without pre-existing disease, although it is unclear whether liraglutide is causative. Further data will be collected in long term outcome trials.<sup>10</sup>

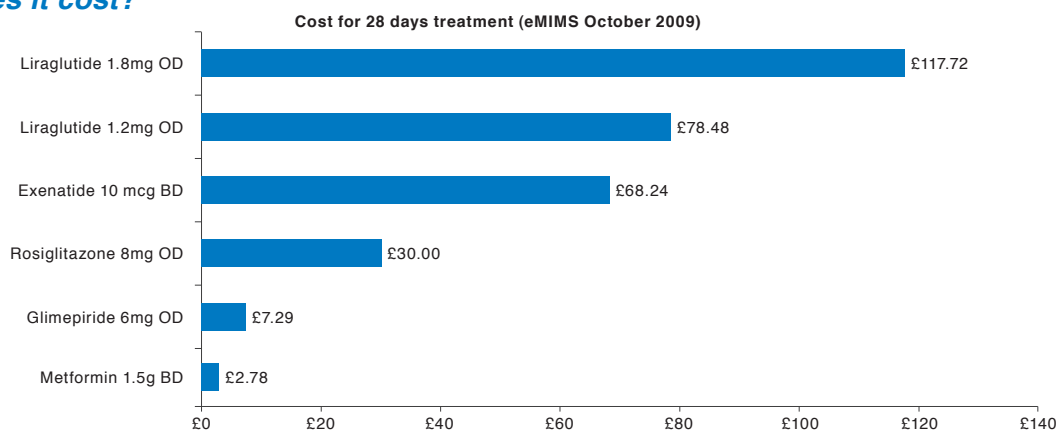
In the exenatide comparison trial,<sup>9</sup> liraglutide patients reported lower AE rates (74.9% vs 78.9% respectively) but the AEs tended to be more serious and severe (serious 5.1% vs 2.6%; severe 7.2% vs 4.7% respectively). No major hypoglycaemia episodes occurred with liraglutide compared with two with exenatide. Twenty six percent of liraglutide patients had minor hypoglycaemia compared with 34% on exenatide.

All suspected adverse reactions to black triangle drugs such as liraglutide should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

Exenatide is similar to liraglutide albeit with more limited indications, and twice daily dosing versus once daily for liraglutide. Only one study has compared them head to head in which a statistically significant improvement in the surrogate endpoint (decrease in HbA<sub>1c</sub>) was seen with liraglutide. NICE guidance (CG87), published in May 2009 did not consider liraglutide as it was not licensed at the time, but recommended that exenatide be considered as 3<sup>rd</sup>

### How much does it cost?



N.B. Doses shown are for general comparison onl and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, G - guideline.

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