

NEW DRUG EVALUATION

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EXENATIDE

Exenatide may be considered as an alternative to insulin or other third-line therapy in obese patients who have failed to achieve adequate glycaemic control on maximal dose oral antidiabetic drugs. Exenatide is an incretin mimetic administered subcutaneously and indicated for use in combination with oral antidiabetic drugs for treatment of type 2 diabetes not controlled with maximal doses of oral therapies. Controlled trials demonstrate a significant reduction in HbA_{1c} in patients concomitantly taking oral antidiabetic drugs with progressive weight loss up to 82 weeks. The most commonly reported side effects were nausea, vomiting and diarrhoea. Clinical efficacy is comparable to insulin therapy but with increased weight loss. However long-term safety data and the effects of exenatide on morbidity and mortality have not yet been demonstrated.

What is it?

Exenatide (Byetta[®], Eli Lilly) is an incretin mimetic licensed for treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.^[1] It is available in either a 5 microgram or 10 microgram solution, for subcutaneous injection via a pen delivery system. It is recommended that therapy should be initiated at 5 micrograms twice daily, for at least one month in order to improve tolerability. If required the dose can be increased to 10 micrograms twice daily to further improve glycaemic control. Exenatide can be administered at any time within the 60-minute period before the morning and evening meal but should not be administered after a meal.^[1]

How effective is it?

Three multi-centre, randomised, triple-blind, placebo-controlled trials examined exenatide's ability to improve glycaemic control in patients with type 2 diabetes who were failing to achieve glycaemic control with maximally effective doses of metformin (n=336),^[2] sulphonylurea (n=377),^[3] or metformin-sulphonylurea combination therapy (n=733).^[4] Patients were randomized to receive either 5 or 10 micrograms exenatide, or placebo twice daily (within 15 minutes before meals) for 30 weeks whilst continuing their existing oral therapy. The primary endpoint was glycaemic control as assessed by glycosylated haemoglobin levels (HbA_{1c}). For patients on the 10 micrograms dose, a 4-week acclimatisation period with 5 micrograms was used to reduce the incidence of nausea. Exenatide treatment significantly reduced HbA_{1c} and mean body weight compared to placebo. On an intention to treat (ITT) basis, significantly more of those patients with an HbA_{1c} > 7% at baseline who received exenatide 10 micrograms in addition to their existing therapy achieved an HbA_{1c} ≤ 7% at 30 weeks: 40% vs. 11% on metformin alone, p<0.01;^[2] 34% vs. 8% on sulphonylurea alone, p<0.0001;^[3] and 30% vs. 7% on metformin-sulphonylurea combination therapy alone, p<0.0001.^[4] The addition of exenatide 10 micrograms significantly improved weight loss at 30 weeks: placebo

subtracted baseline changes of -2.5 kg (with metformin therapy);^[2] -1.0 kg (with sulphonylurea therapy);^[3] and -0.7 kg (with metformin-sulphonylurea combination therapy).^[4] The reduction in HbA_{1c} was sustained and the weight loss continued up to 82 weeks with on going treatment.^[5,6] Only patients with a body mass index (BMI) of ≥27 kg/m² were included in these studies and the extent of weight loss or reduction in HbA_{1c} in patients with a BMI consistent with a healthy weight (20-25 kg/m²) is uncertain.^[2-4]

In a recent study (n=233) exenatide 10 micrograms twice daily was added to existing thiazolidinedione (glitazone) treatment with or without metformin. At 16 weeks exenatide significantly reduced baseline HbA_{1c} (-0.9% vs. +0.1%, p<0.001) and body weight (-1.8 kg vs. -0.2 kg, p<0.001).^[7] However, many patients in this study were receiving sub-maximal doses of metformin and/or glitazone.

In two open label randomised comparisons between exenatide and insulin in patients taking metformin and sulphonylurea, glycaemic control achieved with exenatide (HbA_{1c} decrease of 1.1% and 1.0%) was statistically non-inferior to that achieved with insulin glargine (1.1%) or biphasic insulin aspart (0.9%).^[8,9] Weight loss of 2.3 and 2.5 kg was achieved with exenatide whereas treatment with insulin was associated with weight gain (1.8 and 2.9 kg respectively).^[8,9]

How safe is it?

The most common adverse effects were gastrointestinal with nausea (45-51%), vomiting (12-14%) and diarrhoea (9-17%).^[2-4] Although these effects were common, the frequency and severity decreased in most patients as treatment continued. The incidence of hypoglycaemia was also high in patients concomitantly taking a sulphonylurea (28-36% vs. 3-13% in placebo).^[3,4] When adding exenatide to existing sulphonylurea therapy a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.^[1] The frequency of hypoglycaemia was similar in studies comparing insulin and exenatide.^[8,9] In the three placebo controlled studies 38% of patients had low titre anti-exenatide antibodies at 30 weeks with

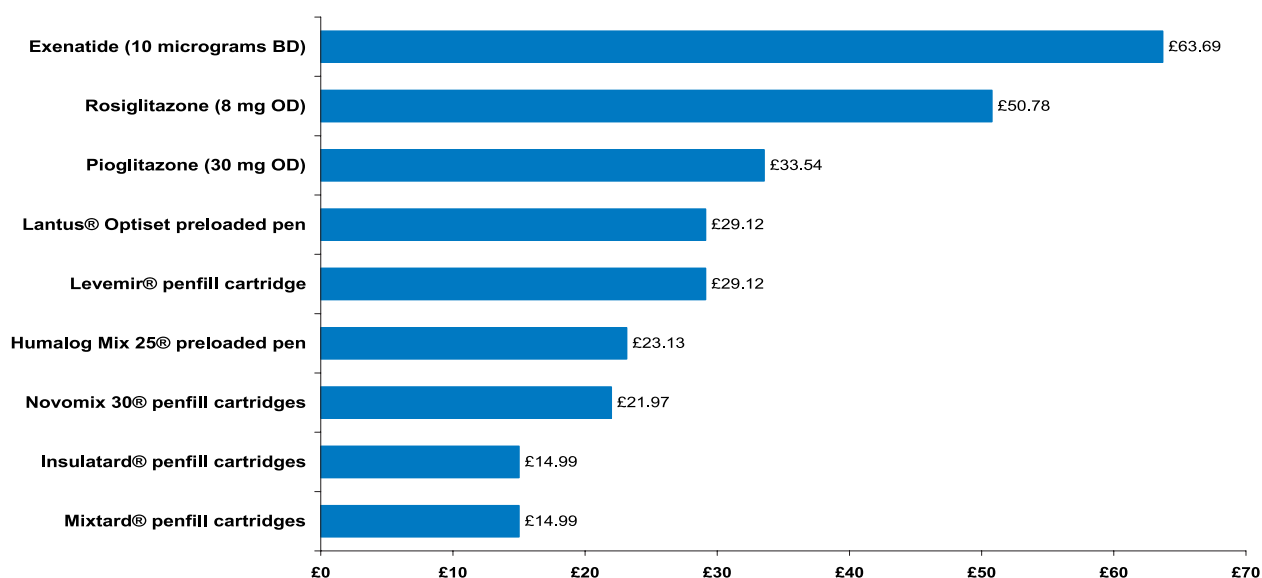
little effect on efficacy. Around 3% of total patients had higher titre anti-exenatide antibodies and no apparent glycaemic response to exenatide treatment.^[1] Due to the possibility of a raised International Normalised Ratio, levels should be monitored during initiation and dose increase of exenatide in patients on warfarin or cumarol derivatives.^[1]

What other options are there?

Drug treatment should only be used to augment the effects of a diet and exercise programme and not to replace them. NICE guidance for type 2 diabetes recommends metformin and sulphonylureas as the first-line therapy for all patients.^[10] A combination of the two drugs should then be used as second-line therapy.^[10] The use of glitazones is only recommended for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the agents.^[11] Although NICE guidelines acknowledge that triple combination therapy (sulphonylurea, metformin and a glitazone) is widely practised in the UK, the licence at that time

How much does it cost?

Cost for 28 days treatment (Drug Tariff/eMIMS August 2007)



N.B. Insulin doses are based on a daily dose of 40IU per day.^[14] Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT – randomised controlled trial; O – open label study; G - guideline

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