

**Exenatide, 5 or 10 micrograms, solution for injection, prefilled pen
(Byetta®) No. (376/07)**

Eli Lilly and Company Limited

8 June 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the 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.

It has shown non-inferiority to two insulin regimens with which it has been compared and has a beneficial effect on weight. It is restricted to use as an alternative to insulin in patients who have failed treatment on metformin and/or sulphonylureas and in whom insulin would be the next treatment option.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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.

Dosing information

Therapy should be initiated at 5 micrograms exenatide per dose, administered twice daily, for at least one month in order to prove tolerability. The dose of exenatide can then be increased to 10 micrograms twice daily to further improve glycaemic control. Doses higher than 10 micrograms twice daily are not recommended.

Each dose should be administered sub-cutaneously in the thigh, abdomen or upper arm at any time within the 60-minute period before the morning and evening meal (or two main meals of the day at least six hours apart) and should **not** be administered after a meal.

Product availability date

01 May 2007

Summary of evidence on comparative efficacy

Exenatide has multiple anti-hyperglycaemic actions and mimics the effects of endogenous incretins which have effects including facilitation of insulin secretion and slowing of gastric emptying.

Six studies have investigated the efficacy of the addition of exenatide 5 or 10 micrograms twice daily to existing oral hypoglycaemic therapy in adult patients with type 2 diabetes mellitus uncontrolled by maximally effective doses of metformin and/or a sulphonylurea. The maximally effective dose of metformin was defined as ≥ 1500 mg/day and for sulphonylureas this was defined for individual agents. Oral hypoglycaemic therapy was continued at the baseline dose, though the dose of sulphonylureas could be adjusted if hypoglycaemia occurred. In all studies the primary end-point was the change from baseline in per-cent glycated haemoglobin (HbA_{1c}) in an intention to treat (ITT) cohort. Secondary end-points included the proportion of patients with HbA_{1c} >7% at baseline who achieved HbA_{1c} $\leq 7\%$, and effects on fasting plasma glucose (FPG) and body weight.

Two randomised open label studies have compared fixed doses of exenatide 10 micrograms twice daily to individually titrated insulin in patients who had failed to achieve glycaemic control on combination therapy with maximally effective doses of metformin and a sulphonylurea. A third study used an open-label crossover design to compare exenatide and insulin glargine over treatment periods of 16 weeks in patients failing to achieve control with metformin or sulphonylurea monotherapy. In all three studies, for the primary end-point, exenatide would be considered non-inferior to insulin if the upper limit of the 95% confidence intervals (CI) for the difference between insulin and exenatide for the change in HbA_{1c} did not exceed 0.4%. This non-inferiority criterion was met in all three studies.

In the first study the comparator was insulin glargine and the change from baseline to week 26 in the least squares (LS) mean HbA_{1c} was -1.11% in the exenatide group, (n=275) from a baseline of 8.18%, compared with -1.11% from a baseline of 8.23% in the insulin glargine group (n=260). This represented a treatment difference of -0.017% (95% CI -0.12 to +0.16).

In the second study the treatment difference between exenatide and biphasic insulin aspart for LS mean HbA_{1c} from baseline to week 52 was -0.15% (95% CI -0.32% to +0.01%). Actual changes were -1.04% from a baseline of 8.6% for exenatide and -0.89% from 8.6% for biphasic insulin aspart.

In the study using an open-label crossover design, data were pooled for the two treatment sequences for each treatment regimen: the changes in LS mean HbA_{1c} were -1.43% and -1.41% respectively. The 95% CI for the treatment difference was -0.2% to +0.15%.

The proportion of patients achieving the target HbA_{1c} was 46% for exenatide compared with 48% for insulin glargine in the first study, 32% for exenatide and 24% with biphasic insulin aspart in the second study and 40% for exenatide compared to 41% for insulin glargine in the crossover study.

Over the three studies changes in FPG were in the range +1.4 to -3.04 mmol/L in the exenatide groups and +2.9 to -4.17 mmol/L in the insulin groups. Body weight decreased in the exenatide groups and increased with insulin in all three studies and the differences between exenatide 10 micrograms twice daily and insulin were significant in two studies where significance levels were reported.

Three 30-week randomised studies involving patients uncontrolled by maximally effective doses of oral hypoglycaemics compared the addition of exenatide 5 or 10 micrograms or placebo to the patient's baseline therapy. Patients had been taking metformin in the first study, sulphonylureas in the second study and a combination of metformin/sulphonylurea in the third.

In all three studies, the addition of exenatide was associated with significant advantages over placebo for the primary end-point (change from baseline in HbA_{1c}) and for secondary end-points including proportion of patients meeting target HbA_{1c} and changes in FPG and body weight.

Although a secondary outcome, change in body weight was studied in all of the above trials. Exenatide given for up to a year was associated with weight loss in the range 0.9 to 2.8kg. This compares to a smaller weight loss with placebo (0.3 to 0.9kg) and with weight gain on insulins (0.35 to 2.9kg). In an extension to three placebo-controlled studies, interim analysis at 82 weeks shows a weight loss of 4.4kg in exenatide-treated patients.

Summary of evidence on comparative safety

The most common treatment-emergent adverse events were gastro-intestinal, particularly nausea and vomiting. In comparative studies, the incidence of nausea ranged from 33% to 57% in exenatide groups compared with 0.4% to 9% in patients treated with insulin analogues; for vomiting the equivalent rates were 9% to 17% and 2.4% to 4% respectively. Nausea and vomiting were generally mild to moderate and were more common in the first weeks of dosing than later in treatment.

In comparative trials the incidence of hypoglycaemia was comparable in exenatide- and insulin-treated groups. When exenatide was used in conjunction with a sulphonylurea (with or without metformin) the incidence of hypoglycaemia was increased over sulphonylurea and placebo. To reduce the risk of hypoglycaemia, the Summary of Product Characteristics recommends that a reduction in the dose of sulphonylurea should be considered.

Summary of clinical effectiveness issues

There are alternatives to exenatide in patients resistant to metformin and/or sulphonylureas with which exenatide has not been compared. In three comparative studies and in one placebo-controlled study, patients initiated adjunctive sub-cutaneous therapy with exenatide, placebo or insulin after failing to achieve control targets with a combination of metformin and a sulphonylurea. In the remaining two studies, patients added exenatide or placebo after failing to gain control on metformin or sulphonylurea monotherapy. Although this is in accordance with the licensed indication, patients in clinical practice who fail to gain control with oral monotherapy have the option to progress to combination oral therapy with metformin and a sulphonylurea, while patients failing on this combination can proceed to triple oral therapy e.g. by adding a thiazolidinedione. Patients were excluded if they had used thiazolidinediones, meglitinides, α -glucosidase inhibitors or exogenous insulin within the prior 3-4 months and the marketing authorisation for exenatide does not recommend co-prescribing it with these agents.

The European Public Assessment Report for exenatide comments that, to prove clinical non-inferiority to insulin, it must be proven that insulin treated subjects had maximally tolerated doses of insulin. It adds that this is doubtful and that, based on the non-blinded nature of these studies, a potential bias towards lower doses of insulin doses cannot be fully excluded, though the applicant has tried to minimise this bias.

Long-term studies are needed to determine the effects of exenatide on disease-related morbidity and mortality.

The dose of exenatide does not need to be adjusted on a day to day basis. However, blood glucose monitoring may still be necessary to adjust the dose of sulphonylureas.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing treatment with exenatide 10 micrograms twice daily with biphasic insulin aspart for patients with type 2 diabetes who had not achieved adequate glycaemic control on maximally tolerated doses of metformin and/or sulphonylureas. A Markov model was used based on the published CORE diabetes model. Patients in the exenatide arm of the model were assumed to be treated with exenatide for three years and then switch to biphasic insulin aspart. The analysis assumed that any weight lost by exenatide patients would be regained when the patient switched to insulin and also that their BMI would rise up to level of insulin treated patients during the first year of the switch. Utility values were taken from the published CODE- 2 study. A time horizon of ten years was adopted. The cost per QALY for this scenario was £6790.

One main issue arose with this analysis. The model compares exenatide to biphasic insulin aspart rather than cheaper forms of insulin. However, additional sensitivity analysis suggests that the ICER versus biphasic human insulin is likely to be cost effective.

Summary of patient and public involvement

Patient Interest Group Submission: Diabetes UK Scotland

Additional information: previous SMC advice

7 April 2006 (Issued August 2006) following an abbreviated submission:

Pioglitazone 15mg/metformin 850mg hydrochloride (Competact[®]) is accepted for restricted use in NHSScotland for the treatment of type 2 diabetes mellitus. It should be used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone. It is restricted to patients who cannot be treated with a sulphonylurea in combination with metformin. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient, though less flexible, dosing regimen.

9 February 2007 following a full submission:

Pioglitazone (Actos[®]), as triple therapy in combination with metformin and a sulphonylurea, is accepted for restricted use within NHS Scotland for the treatment of patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy and where patients are unable or unwilling to take insulin. It should be initiated and monitored only by physicians experienced in the treatment of diabetes mellitus who will be able to identify and manage patients who might benefit.

8 February, 2004 following an abbreviated submission:

Rosiglitazone, metformin (Avandamet[®]) is accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus. It is used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone and cannot be treated with a sulphonylurea in combination with metformin. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient dosing regimen, though less flexible.

06 May 2005 following an abbreviated submission:

Rosiglitazone (Avandia[®]) is accepted for restricted use in NHS Scotland as triple oral therapy in combination with metformin and a sulphonylurea in patients (particularly overweight patients) who are unable to achieve sufficient glycaemic control despite dual oral therapy and where patients are unable or unwilling to take insulin. It should be initiated and monitored only by physicians experienced in the treatment of diabetes mellitus who will be able to identify and manage patients who might benefit.

Additional information: comparators

Acarbose can be used in diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs. Nateglinide and repaglinide can be used in combination with metformin, and repaglinide as monotherapy, in type 2 diabetes mellitus when metformin alone is inadequate.

Pioglitazone and rosiglitazone can be used in type 2 diabetes alone, or in combination with metformin and/or a sulphonylurea.

Additional information: costs

Costs for addition of exenatide to existing therapy of patients inadequately controlled by metformin and/or sulphonylureas are compared below to costs for selected oral antidiabetic agents licensed as add-on therapy.

Add-on costs are also given for insulin products compared to exenatide in clinical trials at doses used in the economic model and for a selection of insulin alternatives.

Costs are not included for continuation of baseline oral therapy therefore any changes, e.g. dose reduction for sulphonylureas, may reduce the costs of the overall regimen.

Drug	Dose regimen	Cost per year (£)
Exenatide	5-10 micrograms sc twice daily	828
<i>Oral therapy</i>		
Rosiglitazone	4-8mg daily	322-660
Pioglitazone	15-30mg daily	314-436
<i>sc insulin</i>		
Insulin glargine	25-40 units per day	237-379
Insulin detemir	25-40 units per day	237-379
Biphasic insulin aspart	25-40 units per day	194-311
Isophane insulin (Humulin I)	25-40 units per day	165-264
Isophane insulin (Insulatard)	25-40 units per day	124-198

sc=sub-cutaneous

Costs are from the eVadis database accessed on 13 March 2007. Doses are for general comparison only and do not imply therapeutic equivalence

Additional information: budget impact

The manufacturer estimated that the net budget impact compared to treatment with biphasic insulin aspart would be £274k in year 1, rising to £1.3m in year 5. This estimate was based on 431 patients in year 1 and 1404 patients in year 5. The manufacturer assumed 20% market share in year 1 rising linearly to 30% in year 5. This assumes that patients are treated for only 3 years with exenatide.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 16 May 2007

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

DeFronzo RA, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28(5):1092-100.

Buse JB, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; 27(11):2628-35.

Kendall DM, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; 28(5):1083-91.

Heine RJ, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005;143(8):559-69.

Heine RJ, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005;143(8):559-69.