Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

exenatide 2mg powder and solvent for prolonged-release suspension for injection (Bydureon®) SMC No. (748/11)

Eli Lilly and Company Limited

09 December 2011

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 once weekly (Bydureon®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of type 2 diabetes mellitus in combination with:

- metformin
- sulphonylurea
- thiazolidinedione
- metformin and sulphonylurea
- metformin and thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

SMC restriction: Exenatide once weekly is restricted to use as a third line treatment option. The economic case for exenatide once weekly for second line use in combination with metformin in place of a sulphonylurea has not been made.

In four randomised comparative studies in patients with type II diabetes and receiving oral anti-diabetic agents and/or diet and exercise regimens, exenatide once weekly was superior to the comparators for change in HbA1c. However in a fifth study exenatide once weekly was not superior to another glucagon-like peptide-1 receptor agonist.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 16 January 2012

Indication

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Dosing Information

The recommended dose is exenatide 2mg once weekly, administered in the abdomen, thigh, or the back of the upper arm as a subcutaneous injection immediately after suspension of the powder in the solvent. It should be administered on the same day each week at any time of day, with or without meals.

The use of exenatide once weekly does not require additional self-monitoring.

Product availability date

July 2011

Summary of evidence on comparative efficacy

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that enhances glucose dependent insulin secretion by the pancreatic beta cell, suppresses inappropriately elevated glucagon secretion and slows gastric emptying. The Scottish Medicines Consortium (SMC) has previously accepted exenatide for restricted use. The current submission is for a new prolonged release formulation that allows once weekly administration.

Five phase III comparator studies (DURATION 1, 2, 3, 5 and 6) have been conducted to evaluate the efficacy of exenatide 2mg administered subcutaneously (sc) once weekly versus various comparators in patients with type II diabetes with an glycosylated haemoglobin (HbA1c) of 7.1 to 11.0% and a body mass index (BMI) of 25 to 45kg/m^2 and < 45kg/m^2 in DURATION 6. [1-5] All studies were open-label with the exception of DURATION 2.

In the 30-week DURATION 1 study and 24-week DURATION 5 study, where patients had previously been treated with diet modification and exercise or with metformin, sulphonylurea, thiazolidinedione or any combination of two of these agents, the comparator was exenatide 10 micrograms sc twice daily. [1,2] In these studies randomisation was stratified by concomitant sulphonylurea use, and baseline HbA1c (<9% versus ≥ 9%). In the 26-week DURATION 2 study, patients had previously been treated with metformin for at least two months and were randomised (stratified by country and baseline HbA1c [<9% versus ≥ 9%]) to add-on treatment with exenatide once weekly, sitagliptin 100mg orally once daily or pioglitazone 45mg orally once daily. [3] In the 26-week DURATION 3 study patients had sub-optimally controlled type II diabetes, despite maximally tolerated doses of metformin or metformin plus sulphonylurea, for at least three months, and were randomised to add-on treatment with exenatide sc once weekly

or insulin glargine sc once daily. The dose of insulin glargine was adjusted to achieve a target glucose of 4 to 5.5mmol/L and injected once daily. Randomisation was stratified by country and oral anti-diabetic treatment (70% metformin only; 30% metformin plus sulphonylurea). In the 26-week DURATION 6 study patients receiving life style modification and oral anti-diabetic drugs were randomised (stratified by sulphonylurea use, baseline HbA1c [<9%; ≥ 9%] and country) to exenatide 2mg sc once weekly or liraglutide 1.8mg sc once daily.

The primary endpoint for all studies was the mean change in HbA1c from baseline to the end of study analysed in the intent-to-treat populations. Exenatide once weekly was superior to comparator arms in all studies with the exception of liraglutide 1.8mg daily in the DURATION 6 study (see table below).

Table; Primary endpoint, change in HbA1c from baseline for the key studies [1-5]

Treatment arms	**n**	**Baseline HbA1c**	**Change in HbA1c to end of study (standard error)**	**Treatment difference; exenatide weekly minus comparator (95% CI)**	**p-value**
DURATION 1; open-label 30 week study					
Exenatide 2mg weekly	148	8.3%	-1.9% (0.08)		
Exenatide 10 microgram bd	147	8.3%	-1.5% (0.08)	-0.33% (-0.54 to -0.12)	p=0.0023
DURATION 5; open-label 24 week study					
Exenatide 2mg weekly	129	8.5%	-1.6% (0.1)		
Exenatide 10 microgram bd	123	8.4%	-0.9% (0.1)	-0.7% (-0.90 to -0.40)	p<0.0001
DURATION 2; double-blind 26 week study					
Exenatide 2mg weekly	160	8.6%	-1.5% 95% CI; -1.7 to -1.4		
Sitagliptin	166	8.5%	-0.9% 95% CI; -1.1 to -0.7	-0.6% (-0.9 to -0.4)	p<0.0001
Pioglitazone	165	8.5%	-1.2% 95% CI; -1.4 to -1.0	-0.3% (-0.6 to -0.1)	p=0.0165
DURATION 3; open-label 26 week study					
Exenatide 2mg weekly	233	8.3%	-1.5% (0.05)		
Insulin glargine	223	8.3%	-1.3% (0.06)	-0.16% (-0.29 to -0.03)	p=0.017
DURATION 6; open-label 26 week study					
Exenatide 2mg weekly	461	8.5%	-1.28% (0.05)		
Liraglutide 1.8mg	450	8.4%	-1.48% (0.05)	0.21% (0.08, 0.34)	p = 0.002

CI=confidence interval, bd= twice daily, nr=not reported

Secondary endpoints included proportion of patients with HbA1c < 7.0% and ≤ 6.5%, weight, systolic blood pressure (SBP) changes and fasting lipids. A higher proportion of patients treated with exenatide once weekly achieved HbA1c < 7.0% and ≤ 6.5% than all comparators, except versus liraglutide 1.8mg daily, in the DURATION 6 study. Liraglutide reduced weight

significantly more than exenatide. In all other studies there was a weight loss for patients on exenatide once weekly and the difference was significant versus sitagliptin, pioglitazone and insulin glargine. Mean SBP significantly decreased from baseline in patients treated with exenatide once weekly in all studies (not reported in DURATION 6) and the difference was significant versus sitagliptin. In three studies there was a significant decrease from baseline in total cholesterol for exenatide once weekly.

There are long term data available for three studies. In DURATION 1, patients entered an open-ended extension phase and all patients received exenatide 2mg once weekly. Approximately two-thirds of the ITT population were treated for three years and a significant mean HbA1c improvement from original baseline was maintained; -1.6%, 95% CI -1.7 to -1.4. [6] In DURATION 2 all patients who entered the open label phase, (approximately three quarters of the original ITT population), received exenatide 2mg once weekly up to week 52. [7] At week 52 the change in HbA1c from original baseline was -1.6 (95% CI -1.9 to -1.3), -1.4 (95% CI -1.7 to -1.2) and -1.6 (95% CI -1.8 to -1.3) in the exenatide/exenatide, exenatide/sitagliptin and exenatide/pioglitazone groups respectively. In DURATION 3 patients continued the treatment originally assigned and 173 patients in each group were treated up to week 84. [8] From week 26 to 84 small increases in HbA1c were observed in both treatment groups; 0.4% versus 0.3% for exenatide and insulin glargine respectively.

Summary of evidence on comparative safety

Injection site reactions, upper respiratory tract infections and gastro-intestinal symptoms including nausea, vomiting, diarrhoea and constipation were the most common adverse events (AE) observed in patients treated with exenatide once weekly.[1-5] Injection site reactions occurred in approximately 16% of exenatide once weekly patients compared to 2% to 7% in the comparator treated patients (which including exenatide twice daily) in safety and efficacy studies overall. [9] There were no reported episodes of major hypoglycaemia in patients on exenatide once weekly in the studies and most cases of minor hypoglycaemia were in patients concurrently receiving a sulphonylurea. [1-5] The summary of product characteristics for exenatide once weekly advises that when exenatide once weekly is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.

There was one case of pancreatitis on exenatide once weekly treatment (DURATION 5 study) which was considered serious, related to treatment and resulted in the patient being withdrawn from the study. [9] Overall four deaths were reported during the exenatide once weekly clinical development program and all were considered unrelated to the treatment. [9]

Summary of clinical effectiveness issues

Four phase III studies (three of which were open-label) have demonstrated the superior efficacy of exenatide 2mg once weekly versus various comparators in the treatment of type II diabetes as measured by change in HbA1c. The European Medicines Agency considered these changes to be clinically relevant. Furthermore, long term extensions of three studies confirmed that the efficacy was maintained for up to three years. In three of the studies treatments were added to oral anti-diabetic medication including metformin, sulphonylureas, thiazolidinediones or a combination of these, which is relevant to the indication under review. However in DURATION

1 and 5 approximately 16% of patients were naïve to drug treatment and receiving diet modification and exercise only.

In one phase III open-label study to test non-inferiority between exenatide once weekly and liraglutide 1.8mg once daily the difference did not meet the non-inferiority criteria. Furthermore there are no head-to-head studies comparing exenatide once weekly with liraglutide 1.2mg daily. In their submission to SMC the company included a network meta-analysis (NMA) to indirectly compare exenatide once weekly with liraglutide 1.2mg daily. This included 19 studies (with common comparators exenatide twice daily, insulin glargine or placebo) and endpoints of HbA1c, weight and SBP were analysed. Results indicate that exenatide once weekly has comparable efficacy to liraglutide 1.2mg once daily.

A weekly sc dose of exenatide (compared to exenatide sc twice daily and liraglutide sc once daily) may potentially offer advantages to the patient who is self-administering in terms of acceptability and compliance and to the service when the district nurse is administering the treatment. However the exenatide weekly formulation is presented as a powder and solvent that requires reconstitution. This differs from the exenatide twice daily and liraglutide preparations that are available as pre-filled pens. After discontinuation of the once weekly preparation the effect of exenatide may continue as plasma levels of exenatide decline over a period of 10 weeks.

There were improvements in a variety of quality of life (QoL) assessments for exenatide once weekly in four studies where QoL data have been published. However there was a higher frequency of injection site reactions with exenatide once weekly than with comparators, including exenatide administered twice daily.[9] Injection site reactions may be managed by symptom relief and changing the site of injection without treatment discontinuation. Other AE were similar for exenatide once weekly to those reported for exenatide twice daily administration. Furthermore, an increase in gastro-intestinal AE in patients switching from exenatide twice daily to once weekly dosing was not observed.

A potential advantage of GLP-1 receptor agonist treatment (exenatide or liraglutide) is weight loss. Other classes of drugs used in this target population are considered to be weight neutral (dipeptidyl peptidase 4 inhibitors) or to cause weight gain (insulin).

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing exenatide once weekly as dual therapy in combination with metformin or pioglitazone as an alternative to sitagliptin and pioglitazone, and as triple therapy in combination with metformin plus sulphonylurea or metformin plus pioglitazone, as an alternative to exenatide twice daily, liraglutide and insulin. Background therapies were assumed to be the same in each arm of the model. SMC clinical experts have suggested that liraglutide and exenatide twice daily are the key comparators.

The CORE diabetes model was used to model the cost and benefits of exenatide once-weekly over a 20-year time horizon. The model structure seemed appropriate and has been used in previous submissions to SMC for type 2 diabetes treatments. Initial treatment was assumed to continue for 3 years before patients switched to insulin glargine for the remainder of the model. The effects of each treatment on key clinical inputs in the model (HbA1c, SBP pressure, total cholesterol, low density lipoprotein- cholesterol, high density lipoprotein-cholesterol and BMI) were taken from the appropriate clinical study where possible, or the network meta-analysis in

the case of the comparison with liraglutide 1.2mg as no direct trial data were available. These treatment effects were then applied to the baseline characteristics of the relevant patient cohort from the clinical studies.

Resource use estimates and utility values used in the model to account for diabetes-related complications were taken from the UK Prospective Diabetes study, supplemented with data from the literature where necessary. The estimates used in the model seem reasonable and were largely consistent with previous submissions to SMC on diabetes medicines.

The results for each of the analyses are presented in the table below:

Exenatide once-weekly versus:	**Incremental cost**	**Incremental quality adjusted life years (QALYs)**	**Cost per QALY**
Exenatide twice daily	-£452	0.092	dominant
Liraglutide 1.8mg	-£1,198	-0.062	£19,239*
Liraglutide 1.2mg	-£172	0.015	dominant
Pioglitazone	£894	0.140	£6,400
Sitagliptin	£644	0.151	£4,262
Insulin glargine	£1,039	0.101	£10,246

*Exenatide is less costly and less effective. Indicates liraglutide 1.8mg would be considered cost-effective versus exenatide once weekly.

The following weaknesses were identified:

- The study comparing exenatide once- weekly with liraglutide 1.8mg did not demonstrate comparable efficacy. The results of the base case analysis indicate that exenatide is less costly but also less effective such that liraglutide 1.8mg would be considered cost-effective versus exenatide once weekly.
- There were no direct trial data comparing exenatide once weekly with liraglutide 1.2mg, which is the dose commonly used in practice. However, the indirect comparison (a network meta-analysis) appears to have been conducted to an acceptable standard and demonstrates that liraglutide 1.2mg and exenatide once weekly have comparable efficacy.
- The base case analysis included non-significant differences in some of the clinical data inputs used in the model. The submitting company were requested to provide an analysis where the non-significant differences were removed. The results of this analysis showed that:
    - Exenatide once weekly was still the dominant treatment when compared with exenatide twice daily.
    - In the comparisons with insulin, pioglitazone and sitagliptin the incremental cost effectiveness ratios increased marginally to £12k, £8k and £5k per QALY respectively.
    - There were no significant differences between exenatide once weekly and liraglutide 1.2mg based on the indirect comparison and the acquisition costs are equivalent.
    - In the comparison with liraglutide 1.8mg, removing the non-significant differences works in favour of exenatide once weekly as liraglutide 1.8mg would no longer be considered cost-effective compared with exenatide once weekly.

In summary, the results indicate that exenatide once weekly is a cost-effective treatment option. When the non-significant differences were removed the conclusions remained robust. As such, the economic case has been demonstrated. However, the economic case for exenatide once weekly in combination with metformin in place of a sulphonylurea has not been made.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Diabetes UK Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 116: Management of diabetes in March 2010. In relation to management of type II diabetes and GLP agonists the following recommendations are made:

- GLP-1 agonists *(exenatide or liraglutide)* may be used to improve glycaemic control in obese adults *(BMI ≥30kg/m^2)* with type 2 diabetes who are already prescribed metformin and/or sulphonylureas. A GLP-1 agonist will usually be added as a third line agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea *(as an alternative to adding insulin therapy).*
- Liraglutide may be used as a third line agent to further improve glycaemic control in obese adults *(BMI ≥30kg/m^2)* with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline no 87; Type II diabetes; the management of type II diabetes in May 2009. It makes the following recommendation in relation to GLP-1 agonists;

Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has:

a. body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
b. BMI < 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Additional information: comparators

Comparators include the GLP receptor agonists, exenatide administered twice daily and liraglutide, as well as pioglitazone, sitagliptin and insulin glargine.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Exenatide (Bydureon®)	**2mg sc once weekly**	**954**
Exenatide (Byetta®)	5 to 10 micrograms sc twice daily	828
Liraglutide	1.2 to 1.8mg sc once daily	952 to 1,428
Sitagliptin	100mg orally once daily	432
Pioglitazone	15 to 45mg orally daily	319 to 488
Insulin glargine	25 to 40 units sc daily	252 to 403

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 20 September 2011, with the exception of insulin glargine where cost taken from MIMS August 2011. sc=subcutaneously. Costs are exclusive of concurrent oral anti-diabetic drugs.

Additional information: budget impact

The company estimated the population eligible for treatment to be 4,099 patients in year 1 rising to 7,235 patients in year 5. Based on an estimated uptake of 30% (1,230 patients) in year 1 and 40% (2,894 patients) in year 5, the impact on the medicines budget was estimated at £1.18m in year 1 and £2.77m in year 5. Assuming some displacement of exenatide twice daily and liraglutide the net medicines budget impact was estimated at £533K and £456K. The fall in the budget impact over time is due to the increase in the displacement of liraglutide which is estimated to be more costly than exenatide once-weekly due to the average dose (1.53mg) used in the budget impact calculations.

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 11 November 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.