Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

lixisenatide 10microgram/0.2mL, 20microgram/0.2mL solution for injection in pre-filled disposable pen (Lyxumia®) SMC No. (903/13)

Sanofi

09 August 2013

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

lixisenatide (Lyxumia®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

SMC restriction: to use in patients for whom a glucagon-like protein-1 (GLP-1) agonist is appropriate, as an alternative to existing GLP-1 agonists.

Lixisenatide reduces glycosylated haemoglobin (HbA1c) and body weight compared with placebo when used in combination with oral antidiabetic drugs or in combination with basal insulin.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

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Indication

Treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

Dosing Information

10microgram subcutaneous injection once daily for 14 days then a maintenance dose of 20microgram subcutaneous injection once daily administered within one hour before the first meal of the day or the evening meal.

Product availability date

4 March 2013

Summary of evidence on comparative efficacy

Lixisenatide is the third glucagon-like protein-1 (GLP-1) agonist marketed in the UK for type 2 diabetes.[1] The other GLP-1 agonists, exenatide (Byetta®), exenatide modified release (Bydureon®) and liraglutide (Victoza®) in combination with oral anti-diabetic drugs (OADs) as defined in their licensed indications have been accepted by SMC for restricted use as third-line pre-insulin treatment options for patients who have not achieved glycaemic control with OADs. Exenatide (Byetta®) has also been accepted for use in combination with basal insulin.[2-6] Within its licensed indication, lixisenatide could be used in second- or third-line treatment of type 2 diabetes and possible comparators would be all other anti-diabetic medicines.[1] However, the company has requested that SMC considers lixisenatide when positioned for use where an alternative GLP-1 agonist is currently used.

The pivotal clinical data are derived from nine of the studies in the GetGoal programme. All studies were double-blind except for a comparison with exenatide, GetGoal-X, which was open-label. They recruited adults with type 2 diabetes for at least one year that was uncontrolled, defined as glycosylated haemoglobin (HbA1c) greater than 7% (but not exceeding 10%) despite stable doses for at least 3 months of anti-diabetic drugs particular to each study: metformin monotherapy in GetGoal-M, GetGoal-F1 and GetGoal-X; metformin ± sulphonylurea in GetGoal-M-Asia; sulphonylurea ± metformin in GetGoal-S; pioglitazone ± metformin in GetGoal-P; basal insulin ± metformin in GetGoal-L; basal-insulin ± sulphonylurea in GetGoal-L-Asia; metformin ± sulphonylurea or glinides ± thiazolidinedione (TDZ) in GetGoal-DUO1. Randomisation was stratified by HbA1c (<8%; ≥8%), and in GetGoal-M, -F1, -X by body mass index (BMI) (<30; ≥30kg/m^2); in GetGoal-P, -S, -L by metformin use; in GetGoal-M-Asia, -L-Asia by sulphonylurea use; and in GetGoal-DUO1 by TZD use. In all studies, except GetGoal-X and -DUO1, patients were randomised to lixisenatide 20micrograms or placebo by subcutaneous (sc) injection within one hour before breakfast, with GetGoal-M also including a group who administered lixisenatide within one hour before evening meal. Lixisenatide was commenced with a two-week, two-step titration (10microgram daily for one week then 15microgram daily for one week), with the GetGoal-F1 study also including a one-step titration group (10microgram daily for two weeks). In GetGoal-X patients were randomised to lixisenatide as described previously or exenatide

10microgram sc twice daily. In GetGoal-DUO1 all patients commenced insulin glargine for a 12-week run and those with HbA1c 7% to 9% and FPG<140mg/dL (7.8mmol/L) were randomised to lixisenatide or placebo as described previously. Baseline anti-diabetics medicines, specified in the inclusion criteria of each study, were continued throughout, except in GetGoal-DUO1, where any sulphonylurea or glinides were discontinued at baseline.[7-16]

The primary endpoint, mean change from baseline to week 24 in HbA1c, was assessed in the modified intention to treat (mITT) population, which included all randomised patients who received at least one dose of study drug and had both baseline and at least one post-baseline assessment of any primary or secondary efficacy variable. An analysis of covariance (ANCOVA) model with treatment group, randomisation strata and country as fixed factors and baseline HbA1c as covariate, and last observation carried forward methodology was used. In the comparison to exenatide the pre-specified non-inferiority margin was 0.4%. The primary outcome was significantly greater with lixisenatide compared to placebo in all studies. In the comparison to exenatide, non-inferiority was demonstrated at the 0.4% margin.[7-16]

Table: HbA1c change from baseline to week 24[7-16]

Study	Lixisenatide		Comparator		Treatment difference (95% CI)
	N	LS mean Change (%)	N	LS mean Change (%)	
Studies in diabetes not controlled with metformin monotherapy					
GG-X	315	-0.79	315	-0.96	0.17 (0.033 to 0.297)
GG-M	255	-0.87[a]	170	-0.38	-0.48 (-0.66 to -0.31)
	255	-0.75[b]			-0.37 (-0.54 to -0.19)
GG-F1	160	-0.83[c]	159	-0.42	-0.41 (-0.58 to -0.23)
	160	-0.92[d]			-0.49 (-0.67 to -0.32)
Studies in diabetes not controlled with one or two oral anti-diabetic drugs					
GG-S	570	-0.85	286	-0.10	-0.74 (-0.87 to -0.62)
GG-M-Asia	195	-0.83	193	-0.47	-0.36 (-0.55 to -0.16)
GG-P	320	-0.90	159	-0.34	-0.56 (-0.73 to -0.39)
GG-DUO1*	223	-0.71	223	-0.40	-0.32 (-0.46 to -0.17)
Studies in diabetes not controlled with basal insulin					
GG-L	327	-0.74	166	-0.38	-0.36 (-0.55 to -0.17)
GG-L-Asia	154	-0.77	157	0.11	-0.88 (-1.12 to -0.65)

GG = GetGoal; a = lixisenatide in the morning; b = lixisenatide in the evening; c = lixisenatide 2-step titration; d = lixisenatide 1-step titration; CI = confidence interval; Comparator = placebo in all studies, except GG-X, where the comparator was exenatide 10microgram twice daily. * GG-DUO1 included a 12-week run-in where all patients commenced treatment with insulin glargine.

In all placebo-controlled studies the proportion of patients achieving HbA1c ≤7% at week 24 was significantly greater with lixisenatide, with values ranging from 28% to 56% compared to 5.2% to 39% with placebo. In GetGoal-X the proportions were similar in the lixisenatide and exenatide groups: 48% and 50%, respectively.[7-16]

Mean body weight from baseline to week 24 was reduced with lixisenatide in all studies except GetGoal-DUO1, where there was a small increase. The mean weight changes with lixisenatide were significant compared to placebo in GetGoal-F1, -S, -DUO1, and -L (but not in GetGoal-M, -P, -M-Asia, and -L-Asia). Overall the mean difference in body weight compared to placebo was approximately 1kg. Mean body weight reduction from baseline to week 24 with lixisenatide was

significantly less than with exenatide: 2.96kg versus 3.98kg, treatment difference 1.02kg (95% CI: 0.46 to 1.58).[7-16]

Summary of evidence on comparative safety

The overall adverse effect profile is typical of a GLP-1 agonist, with gastrointestinal adverse effects being the most common. In the comparison to exenatide, there were similar rates of adverse events (70% and 72%) and serious adverse events (2.8% and 2.2%). Rates of adverse events leading to discontinuation (10% versus 13%), gastrointestinal disorders (43% versus 51%), vomiting (10% versus 13%) and diarrhoea (10% versus 13%) were slightly lower with lixisenatide and rates of nausea (24% versus 35%) and symptomatic hypoglycaemia (2.5% versus 7.9%) were significantly lower.[7-16]

Summary of clinical effectiveness issues

Lixisenatide reduced HbA1c and body weight compared to placebo when used in combination with various OADs and in combination with basal insulin. The magnitude of the treatment effect was considered to be clinically relevant by the EMA, although some additional analyses were conducted to support this conclusion. For add-on to metformin, post-hoc analyses of patients recruited in Europe indicated a mean placebo-corrected reduction in HbA1c of approximately 0.5%. For add-on to insulin, subgroup analyses of patients expected to adhere to background therapy indicated that a reduction in HbA1c of 0.5 to 0.6% compared to placebo was plausible. There was a similar magnitude of effect, 0.56%, in GetGoal-P, where lixisenatide was added-on to pioglitazone ± metformin. In GetGoal-S, where lixisenatide was added-on to sulphonylurea ± metformin, a larger effect of 0.74% was observed. It is possible that this was influenced by the larger proportion of Asian patients in this study (approximately 45%), as the glucose-lowering effect of lixisenatide is more pronounced in Asian compared to Caucasian patients. The magnitude of treatment effects in this study and the two studies that recruited entirely Asian patients, GetGoal-M-Asia and -L-Asia, may not be achieved in practice in the mainly Caucasian population in Scotland.[7-16]

The primary outcome, HbA1c, is an established measure of blood glucose control over the preceding two to three months. The way in which HbA1c results are expressed in the UK has changed recently; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.5% are 48mmol/mol and 58mmol/mol in the new units, with the non-diabetic reference range of 4% to 6% being 20mmol/mol to 42mmol/mol.

Liraglutide is the most commonly prescribed GLP-1 agonist.[43] A mixed treatment comparison (MTC) was presented to compare lixisenatide to liraglutide. This included 28 studies, only 11 of which included either of these two treatments. The validity of the comparison was limited by numerous issues, including apparent inconsistencies and lack of clarity around the study selection process and MTC model and heterogeneity across the included studies in terms of design, inclusion and exclusion criteria, baseline characteristics and definition of outcomes, such as hypoglycaemia.[7-11,13,18-40] A comparison of lixisenatide to liraglutide 1.8mg was not presented.

For the other GLP-1 agonist, exenatide, an assumption of clinical equivalence when used in combination with OADs is based on the direct comparative study (GetGoal-X).[8] During the EMA

review it was noted that the upper limit of 95% confidence interval (CI) for difference in reduction of HbA1c with exenatide compared to lixisenatide in the mITT population, of 0.297%, was within their recommended non-inferiority margin of 0.3%. However, the EMA have also noted the upper limit of the 95% CI was 0.315% in the completer population: along with the significantly reduced effect on weight loss with lixisenatide the EMA commented that non-inferiority to exenatide has not been robustly shown when both these factors are considered.[7]

A Bucher pair-wise indirect comparison of lixisenatide to exenatide twice daily in combination with basal insulin was presented. This included data from GetGoal-L and a 30-week double-blind placebo-controlled study of exenatide in patients with type 2 diabetes not controlled by insulin glargine ± metformin or pioglitazone or both OADs.[7,15,17] There were numerous significant sources of heterogeneity between the two studies that limit the validity of the results.

The company propose that lixisenatide be used for patients failing to achieve glycaemic control on two OADs. For the majority of people in the Scotland, the two OADs would be metformin and a sulphonylurea. Only two studies could recruit these patients, GetGoal-S and M-Asia. These had 85% and 45%, respectively, of the study population receiving both drugs at baseline. However, 45% and 100% of patients in the respective studies were Asian people, in whom lixisenatide has an enhanced effect. This limits the application of results.[7,11,12]

The GetGoal studies recruited limited numbers of patients aged over 75 years (n=56), therefore, there may be some uncertainty about extrapolation of results to this group.[7]

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submitting company presented cost-minimisation analyses comparing lixisenatide to other GLP-1 agonists, either in combination with OADs or in combination with basal insulin. The population of interest was patients uncontrolled on two OADs and/or basal insulin, when the use of a GLP-1 agonist is appropriate.

In combination with OADs, lixisenatide is compared to exenatide twice daily and liraglutide 1.2mg. In combination with basal insulin, lixisenatide is compared to exenatide twice daily. The time horizon was one year; however, cost savings were also estimated for 5 years. Prescribing data suggest that the predominant comparator is liraglutide.

A scenario comparing two alternative treatment pathways, with treatment to HbA1c target as the outcome of interest was also presented. In pathway A, patients receive lixisenatide as the first line GLP-1 agonist option followed by liraglutide 1.2 mg for those not achieving their HbA1c target. This was compared to pathway B where all patients are treated with liraglutide 1.2mg. The time horizon for this analysis was three years.

The clinical evidence to support the use of a cost-minimisation analysis comparing lixisenatide versus exenatide twice daily, in combination with OADs, came from a randomised, open-label, active-controlled, parallel-group, multicentre study that compared the efficacy and safety of lixisenatide once daily with exenatide twice daily, each as add-on therapy in type 2 diabetes mellitus patients inadequately controlled on metformin monotherapy. In this study, lixisenatide demonstrated non-inferiority to exenatide twice daily in terms of reduction in HbA1c. A Bucher

pair-wise indirect comparison of lixisenatide to exenatide in combination with basal insulin was presented. A further indirect comparison was used to compare lixisenatide with liraglutide 1.2mg in combination with OADs.

In terms of resource use, the analyses compared the cost per year per patient and included medication and needle costs only.

The results showed that lixisenatide is associated with a total cost (including needles) per year per patient of £739 versus £898 for exenatide twice daily (£705 versus £830 based on drug costs only). Lixisenatide is therefore associated with a 21.4% cost saving per patient per year of £159. The results also showed that lixisenatide is associated with a total cost per year per patient of £705 versus £955 for liraglutide 1.2mg. Lixisenatide is therefore associated with a 35.3% cost saving per patient per year of £250. On the basis of these results, the submitting company stated that lixisenatide was the preferred treatment on cost-minimisation grounds.

The results of the analysis comparing pathway A versus B show that pathway A (lixisenatide followed by liraglutide in those not achieving their HbA1c target) costs an average of £2,514 per patient over the course of three years, while treatment with liraglutide for 3 years costs £2,865 per patient per year. Therefore, the company asserted that treating patients with lixisenatide first-line could deliver savings of £350 per patient over three years.

Limitations of the analyses related to the weaknesses noted above in relation to the clinical studies and MTC upon which the economic analyses are based. In particular, in the comparison against exenatide, while non-inferiority had been demonstrated in terms of HbA1c, weight reduction with lixisenatide was significantly less than with exenatide. As seen in other economic evaluations in diabetes, it could be argued that these weight changes result in quality-adjusted life-year (QALY) and cost implications which have not been accounted for here and which means the assumption of equivalence necessary for the cost-minimisation analysis is not strictly supported. However, the company has estimated that any differences in utility caused by weight change differences would be very small.

In the comparison with liraglutide, the cost-minimisation analyses results presented above have some weaknesses given the outputs of the MTC. Further, in relation to the pathway analysis against liraglutide, some other limitations are noted. No account is taken of any health detriments patients may experience if they do not achieve their target on lixisenatide and before they are switched to liraglutide. In addition, SMC experts were asked to comment on clinical appropriateness and willingness to use a pathway where patients are treated in such a sequenced manner. The comments received suggest some reluctance to adopt such a strategy. Given these issues, the cost-effectiveness case against liraglutide is weaker than the case against exenatide.

Overall, despite these weaknesses the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was received from Diabetes UK.

Additional information: guidelines and protocols

In March 2010 the Scottish Intercollegiate Guidelines Network (SIGN) published Management of Diabetes: a national clinical guideline. These were revised in May 2011. They recommend 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. A best practice point is also made that careful judgment must be applied in relation to people with long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years, these individuals being poorly represented in published studies) to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 agonists.[41]

In May 2009 the National Institute for Health and Care Excellence (NICE) published clinical guideline number 87, Type 2 diabetes: the management of type 2 diabetes. This makes a recommendation to consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulphonylurea 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) ≥35kg/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 a BMI <35kg/m^2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. Only continue GLP-1 mimetic (exenatide) if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and weight loss of at least 3% of initial body weight at 6 months).[42]

Additional information: comparators

Lixisenatide could be used as second- or third-line treatment of type 2 diabetes and possible comparators would be all anti-diabetic medicines.[1] However, the company has requested that SMC considers lixisenatide for situations where an alternative GLP-1 agonist would be used and in this context the comparators would be the two other drugs in this class, liraglutide and exenatide.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Lixisenatide	**20microgram once daily**	**704**
Liraglutide	1.2 to 1.8mg once daily	952 to 1,428
Exenatide m/r	2mg once weekly	954
Exenatide	5 to 10microgram twice daily	828

Doses are for general comparison and do not imply therapeutic equivalence. All drugs administered via subcutaneous injection. Costs from eVadis on 17 April 2013.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 126,000 in year 1 rising to 142,527 in year 5, with an estimated uptake rate of 1.01% in year 1 and 3.44% in year 5. The company has also estimated that there will be a discontinuation rate of 20.62% in all years.

The gross impact on the medicines budget was estimated to be £715.6k in year 1 and £2.748m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be a saving of £197.3k in year 1 and a saving of £757.7k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 12 July 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.