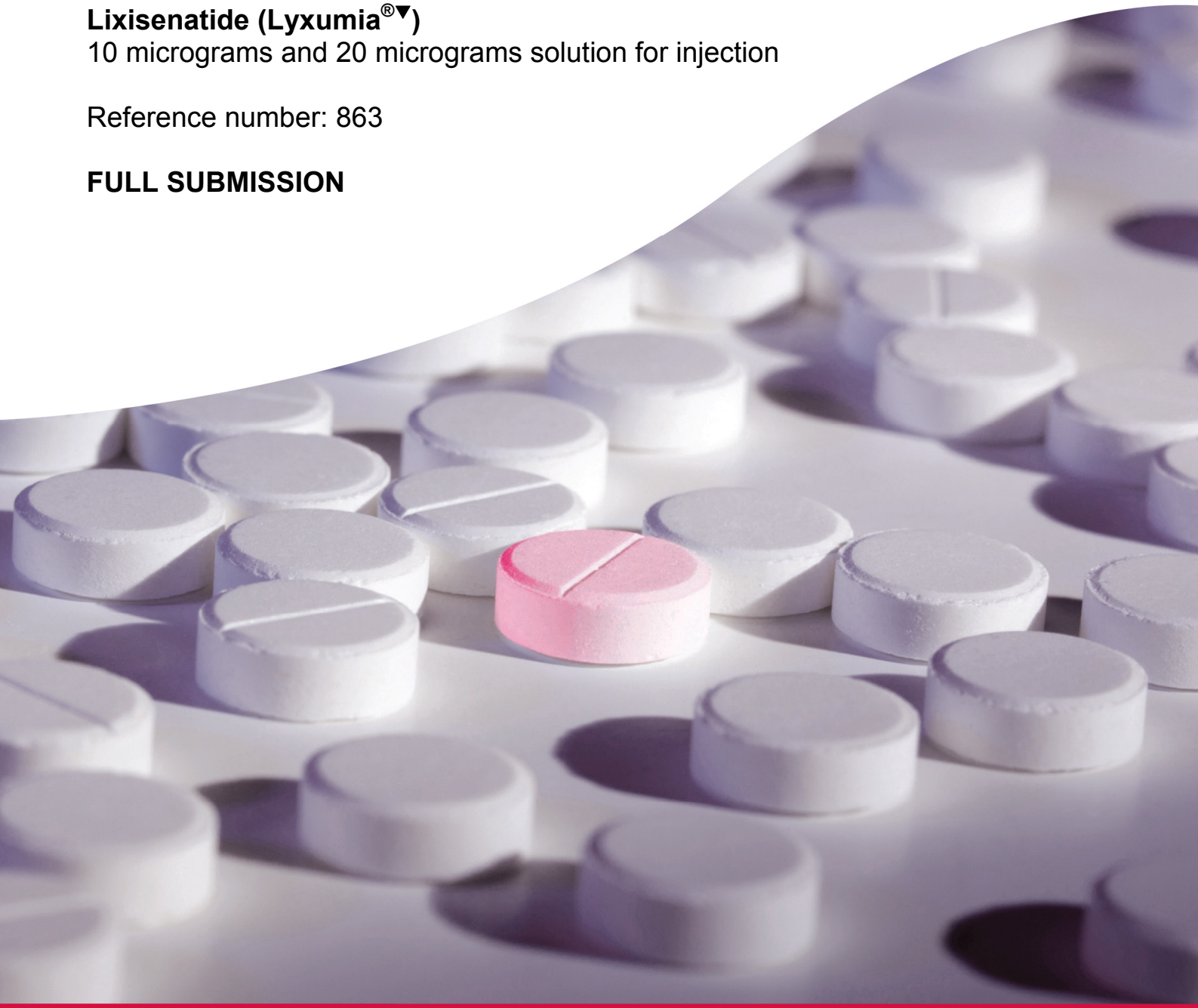
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Lixisenatide (Lyxumia®▼)
10 micrograms and 20 micrograms solution for injection

Reference number: 863

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Lixisenatide (Lyxumia®▼)
10 micrograms and 20 micrograms solution for injection

This assessment report is based on evidence submitted by Sanofi-Aventis Ltd on 24 July 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lixisenatide (Lyxumia®▼) is indicated for the 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[2,3].
Dosing	Lixisenatide is administered once daily by subcutaneous injection in the thigh, abdomen or upper arm, within the hour prior to the first meal of the day or the evening meal. Dosing is initiated at 10 micrograms lixisenatide once daily for 14 days, and continues on a fixed maintenance dose of 20 micrograms lixisenatide once daily from day 15[2,3]. When lixisenatide is added to existing metformin therapy, the current metformin dose can be continued unchanged. When lixisenatide is added to existing therapy of a sulphonylurea or basal insulin, a reduction in the dose of the sulphonylurea or the basal insulin may be considered to reduce the risk of hypoglycaemia. Lixisenatide should not be given in combination with both basal insulin and a sulphonylurea due to increased risk of hypoglycaemia[2,3]. Refer to the Summary of Product Characteristics (SPC) for further information regarding lixisenatide dosing[2,3].
Marketing authorisation date	1 February 2013[2,3].

2.0 DECISION CONTEXT

2.1 Background

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disorder that is caused by insufficient insulin production by pancreatic cells, or the inability of the body to properly utilise endogenous insulin (insulin insensitivity or resistance)[4,5]. Of the 167,537 diabetes patients in Wales, around 85% have T2DM[5,6]. T2DM is associated with increased cardiovascular risk and microvascular complications such as eye, nerve, and renal damage[4,7].

NICE Clinical Guidelines recommend that patients with T2DM trial the use of lifestyle interventions, such as diet modification and exercise, as first line treatment[7–9]. Metformin therapy is recommended in overweight or obese patients where blood glucose is inadequately controlled (glycosylated haemoglobin [HbA_{1c}] levels ≥ 6.5% [48 mmol/mol; see Glossary] or agreed target) after lifestyle interventions. If blood glucose control remains or becomes inadequate, another oral antidiabetic medication

(usually a sulfonylurea) should be added to metformin therapy. A glucagon-like peptide 1 (GLP-1) mimetic, such as exenatide (Byetta®; Bydureon®) or liraglutide (Victoza®), is recommended as a third-line therapy when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% [59 mmol/mol] or agreed target) in specific patient groups and under certain circumstances*. Treatment with a GLP-1 mimetic should be continued only if the patient has a reduction in HbA_{1c} of ≥ 1.0 percentage point and a decrease of ≥ 3% of initial body weight in six months. Insulin therapy should be initiated following therapy with other measures where control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% [59 mmol/mol] or agreed target). However, where a patient receiving dual therapy is markedly hyperglycaemic, insulin therapy should be initiated in preference to addition of other treatments to the therapeutic regimen[7,8].

Lixisenatide is a GLP-1 receptor agonist and acts to stimulate insulin secretion when blood glucose is increased, suppress glucagon secretion and slow gastric emptying, thereby reducing the rate at which meal-derived glucose enters the circulation[2,3]. Lixisenatide is indicated for the treatment of T2DM patients 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[2,3]. However, the applicant company has suggested that lixisenatide should be placed as a treatment option for patients uncontrolled on two or more oral antidiabetic medications, consistent with the place in therapy of existing GLP-1 mimetic treatments as recommended by NICE Clinical Guideline (CG) 87[1,7,8]. In addition, the applicant company has requested that lixisenatide should be considered as a treatment option in patients uncontrolled on basal insulin, in line with the licensed indication[1–3].

2.2 Comparators

The comparators included in the company submission were:

- For use in combination with oral glucose-lowering products:
  - Exenatide (Byetta®)
  - Liraglutide (Victoza®)
- For use in combination with basal insulin:
  - Exenatide (Byetta®)

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Blood-glucose-lowering therapy for type 2 diabetes (2013)[8].
- American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach (2012)[9].
- NICE. Technology Appraisal (TA) 248. Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (2012)[10].
- NICE. TA203. Liraglutide for the treatment of type 2 diabetes mellitus (2010)[11].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116 (2010)[12].
- NICE. CG 87. Type 2 diabetes: the management of type 2 diabetes (2009)[7].
- NICE. CG66. Type 2 diabetes: national clinical guideline for management in primary and secondary care (2008)[4].
- Welsh Government. National service framework for diabetes (Wales): standards (2003)[5].

* Patients with a body mass index (BMI) ≥ 35 kg/m^2 in people of European descent if there are specific problems associated with high body weight, or a BMI < 35 kg/m^2 where insulin treatment is unacceptable because of occupational implications or weight loss would benefit other comorbidities. Refer to NICE guidelines for further information[7,8].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of exenatide:

- In the absence of a submission from the holder of the marketing authorisation, exenatide (Byetta®) cannot be endorsed for use within NHS Wales as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents (2012)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of the clinical effectiveness of lixisenatide in combination with oral glucose-lowering medicinal products in patients where these do not provide adequate glycaemic control, the company submission includes a phase III study (GetGoal-X) comparing lixisenatide with exenatide, a phase II pharmacokinetic study comparing lixisenatide with liraglutide (study PDY10931) and a mixed treatment comparison (MTC) evaluating lixisenatide against liraglutide[1]. The company submission also includes a placebo-controlled phase III study (GetGoal-L), evaluating lixisenatide in combination with basal insulin and metformin, which is used to inform an indirect comparison against exenatide in combination with basal insulin[1].

Additionally, the applicant company has provided several placebo-controlled supporting studies; however, these studies do not provide evidence of the effectiveness of lixisenatide in comparison with a relevant comparator for the indication under consideration, and so the studies will not be discussed further[1].

3.1 GLP-1 mimetics in combination with oral glucose-lowering products

3.1.1 GetGoal-X

This phase III, randomised, parallel-group, open-label, multicentre, noninferiority study conducted over 24 weeks evaluated the efficacy and safety of lixisenatide versus exenatide in T2DM patients (21–84 years) inadequately controlled on metformin[14]. Patients (n = 639) were randomised (1:1) to receive either lixisenatide once-daily (administered one hour before the morning meal, initiated as 10 micrograms for one week, followed by 15 micrograms for one week, then a maintenance dose of 20 micrograms for the remainder of the study) or exenatide twice-daily (administered and titrated as per SPC[15])[14]. Participants continued to receive their previous metformin dose (≥ 1.5 g/day) throughout the study[14].

The primary efficacy endpoint was the absolute change in HbA_{1c} from baseline to Week 24, while secondary efficacy measures included the percentage of participants attaining HbA_{1c} < 7.0% at week 24 and changes in body weight from baseline to week 24. In the modified intent-to-treat population (mITT) population, the least squares (LS) mean change in HbA_{1c} was −0.79% in lixisenatide-treated patients and −0.96% in the exenatide group, with a treatment difference of 0.17% (95% confidence interval [CI]: 0.033–0.297); this fulfilled the prespecified criterion for demonstration of noninferiority of lixisenatide to exenatide (the upper limit of the 95% CI less than 0.4). This was supported by several secondary endpoints (see Table 1). However, LS mean change in body weight was greater in patients receiving exenatide, although reductions were seen in both groups (−2.96 kg in the lixisenatide group versus −3.98 kg in exenatide-treated patients)[14].

During a long-term safety extension period of at least 52 weeks, reductions in HbA_{1c} were maintained[1] and the proportions of patients who needed rescue therapy were 19.4% and 16.2% in the lixisenatide and exenatide groups[16].

Table 1. Overview of key endpoints from GetGoal-X and PDY10931 studies[14,17].

	GetGoal-X			PDY10931		
	Lixisenatide	Exenatide	Difference (95% CI)	Lixisenatide	Liraglutide	Difference
n	315	315	-	77	71	-
Mean change in HbA_{1c} from baseline to end of study period (%)	−0.79	−0.96	0.17 (0.033 to 0.297)	−0.32	−0.51	0.19 p < 0.01
Percentage attaining HbA_{1c} < 7.0% at end of study period (%)	48.5	49.8	−1.0 (−8.51 to 6.51)	Not reported	Not reported	Not reported
Mean change in body weight from baseline to end of study period (kg)	−2.96	−3.98	1.02 (0.456 to 1.581)	−1.6	−2.4	0.8 p < 0.01

3.1.2 Study PDY10931

This phase II, randomised, parallel-group, open-label, multicentre study conducted over 28 days evaluated the pharmacodynamics of lixisenatide versus liraglutide in T2DM patients (aged 37–74 years) inadequately controlled on metformin[17]. Patients were randomised (1:1) to receive either lixisenatide (n = 77) or liraglutide (n = 71), administered and titrated as per the respective SPCs[2,3,17,18].

The primary efficacy endpoint was the change from baseline to day 28 in postprandial glucose (PPG) from the start of breakfast (30 minutes after injection of study treatment) until four hours later, as evidenced by the area under the plasma glucose concentration-time curve ($AUC_{0:30–4:30h}$)[17]. Lixisenatide-treated patients exhibited a significantly greater reduction in PPG compared with those that received liraglutide (−12.6 h/mmol/l versus −4.0 h/mmol/l; p < 0.0001). Although both treatments groups exhibited reductions from baseline in mean HbA_{1c} and body weight, these changes were significantly smaller in the lixisenatide group (mean HbA_{1c}: −0.32% versus −0.51%, p < 0.01; body weight: −1.6 kg versus −2.4 kg, p < 0.01)[17].

3.1.3 Mixed treatment comparison

As the data directly comparing lixisenatide with liraglutide in T2DM patients in combination with oral antidiabetic medications was limited, a systematic review and MTC utilising a Bayesian network analysis method have been included in the company submission to evaluate the relative efficacy of these treatments[1].

The systematic review identified all randomised controlled trials conducted over 20–30 weeks that compared GLP-1 analogues in adult T2DM patients, regardless of trial design (parallel, crossover, open label, single or double blind). Studies must have reported a relevant outcome, which included mean change in HbA_{1c} from baseline, mean body weight change from baseline and proportion of patients achieving an HbA_{1c} target of ≤ 7% or ≤ 6.5%[1].

Bayesian random-effects MTC analyses were conducted for several continuous and binary outcomes, including HbA_{1c} and weight. The results comparing outcomes for lixisenatide versus liraglutide are presented in Table 2. [Commercial in confidence data removed]

Table 2. Overview of MTC outcomes for lixisenatide versus liraglutide.

[Commercial in confidence data removed]

3.2 GLP-1 mimetics in combination with basal insulin

As there were no data directly comparing lixisenatide to exenatide T2DM patients uncontrolled on basal insulin, an indirect treatment comparison has been included in the company submission to evaluate the relative efficacy of the two treatments[1].

3.2.1 GetGoal-L

This phase III, randomised, parallel-group, placebo-controlled, double-blind study conducted over 24 weeks evaluated the efficacy and safety of adding lixisenatide to established basal insulin therapy with or without metformin in T2DM patients (aged 29–81 years) not yet achieving adequate glycaemic control[19]. Patients (n = 495) were randomised (2:1) to receive either lixisenatide or placebo, where lixisenatide is administered once daily one hour before the morning meal, initiated as 10 micrograms for one week, followed by 15 micrograms for one week, then a maintenance dose of 20 micrograms (if tolerated) for the remainder of the study. If used at enrolment, metformin was continued at a stable dose throughout the study; basal insulin dosage was also unchanged except to limit hypoglycaemia[19].

The LS mean change in HbA_{1c} from baseline to week 24 (primary endpoint) was −0.74% in lixisenatide-treated patients and −0.38% in the placebo group (difference: −0.36%; 95% CI: −0.550 to −0.174)[16]. This was supported by several secondary endpoints, where similar improvements were demonstrated in the lixisenatide group (see Table 3). Rescue therapy with rapid-acting insulin or increased basal insulin was required by 19 (6%) of lixisenatide patients and 12 (7%) of the placebo group (p = 0.540)[19].

Table 3. Overview of key endpoints from GetGoal-L and GWCO[19–21].

	GetGoal-L			GWCO		
	Lixisenatide	**Placebo**	**Difference (95% CI)**	**Exenatide**	**Placebo**	**Difference (95% CI)**
n	327	166	-	137	122	-
Mean change in HbA_{1c} from baseline to end of study period (%)	−0.74	−0.38	−0.36 (−0.550 to −0.174) p = 0.0002	−1.74	−1.04	−0.69 (−0.93 to −0.46) p < 0.001
Percentage attaining HbA_{1c} < 7.0% at end of study period (%)	28.3	12.0	16.3 p < 0.0001	56	29	27 p < 0.001
Mean change in body weight from baseline to end of study period (kg)	−1.80	−0.52	−1.28 (−1.803 to −0.747) p < 0.0001	−1.78	0.96	−2.74 p < 0.001

3.2.2 Indirect comparison between lixisenatide and exenatide

The comparison utilised the Bucher adjusted indirect comparison method and included data from the GetGoal-L study (see Section 3.2.1)[19] and study GCWO[20,21].

Study GCWO was a phase III, randomised, parallel-group, placebo-controlled, double-blind study conducted over 30 weeks, which evaluated efficacy and safety of adding exenatide to established basal insulin therapy (as insulin glargine) with or without metformin or pioglitazone (or both) in T2DM patients (≥ 18 years)[21,22]. Patients (n = 261) were randomised to receive either exenatide or placebo, administered and

titrated as per the SPC[15,21]. Patients continued to use prestudy doses of oral antihyperglycaemic agents; insulin glargine dosage remained unchanged (except to limit hypoglycaemia) for five weeks, after which doses were titrated to achieve fasting plasma glucose (FPG) levels < 5.6 mmol/l[21].

The LS mean change in HbA_{1c} from baseline to week 30 (primary endpoint) was −1.74% in exenatide-treated patients and −1.04% in the placebo group (difference: −0.69%; 95% CI: −0.93 to −0.46). This was supported by several secondary endpoints, where similar improvements were demonstrated in the exenatide group (see Table 3)[21].

The endpoints evaluated for the adjusted indirect comparison were mean HbA_{1c} change from baseline to end of study period, the proportion of patients achieving a HbA_{1c} target < 7% and mean change from baseline in body weight (see Table 4)[1]. [Commercial in confidence data removed]

Table 4. Summary of the main outcomes of the indirect treatment comparison between lixisenatide and exenatide[1].

Outcome	Treatment comparison	Endpoint (95% CrI)
Mean HbA_{1c} change from baseline to end of study period (%)	Lixisenatide versus placebo	−0.36 (−0.65 to −0.07)
	Exenatide versus placebo	−0.70 (−0.95 to −0.45)
	Lixisenatide versus exenatide	*
Patients achieving a HbA_{1c} target < 7% (odds ratio; OR)	Lixisenatide versus placebo	2.89 (1.68 to 4.95)
	Exenatide versus placebo	3.19 (1.90 to 5.35)
	Lixisenatide versus exenatide	*
Mean body weight change from baseline to end of study period (kg)	Lixisenatide versus placebo	−1.28 (−2.07 to −0.49)
	Exenatide versus placebo	−2.74 (−3.77 to −1.71)
	Lixisenatide versus exenatide	*
* Commercial in confidence figures removed.		

3.3 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of lixisenatide is largely similar to other products in the class, with gastrointestinal AEs most common[16]. CHMP also noted several GLP-1 agonist class effects, including potential risks associated with a propensity to induce increased heart rate, pancreatitis and allergic reactions, which are reflected in the SPC and will be studied post marketing[16].

3.3.1 GLP-1 mimetics in combination with oral glucose-lowering products

3.3.1.1 Lixisenatide versus exenatide

The overall incidence of patients reporting AEs and serious AEs (SAEs) during the 24-week GetGoal-X initial treatment period were similar in the lixisenatide and exenatide treatments groups (AEs: 221/318 [69.5%] versus 228/316 [72.2%], respectively; SAEs: 9/318 [2.8%] versus 7/316 [2.2%], respectively)[14]. Discontinuations due to AEs occurred in 33 (10.4%) lixisenatide-treated patients versus 41 (13.0%) patients in the exenatide group; this was commonly due to gastrointestinal symptoms (20 [6.3%] versus 24 [7.6%], respectively). One death was reported in each treatment group[14].

The most common AEs in both treatment groups were gastrointestinal by nature and occurred less often in lixisenatide-treated patients than in the exenatide group (gastrointestinal disorders: 137 [43.1%] versus 160 [50.6%]; nausea: 78 [24.5%] versus 111 [35.1%]; vomiting: 32 [10.1%] versus 42 [13.3%]; diarrhoea: 33 [10.4%] versus 42 [13.3%]). Additionally, significantly fewer patients experienced symptomatic

hypoglycaemia in the lixisenatide group compared with exenatide (2.5% versus 7.9%; p < 0.05). However, 27 (8.5%) lixisenatide-treated patients reported injection site reactions, compared with 5 (1.6%) in the exenatide group[14].

Analysis of data from the on-treatment period for the entire GetGoal-X study (mean treatment period: 495 days in lixisenatide group and 483 in exenatide patients) supports data from the initial treatment phase[1].

3.3.1.2 Lixisenatide versus liraglutide

The incidence of patients reporting AEs during study PDY10931 was lower in lixisenatide-treated patients than those that received liraglutide (45/77 [58.4%] versus 52/71 [73.2%])[17]. This difference was mainly due to a lower incidence of gastrointestinal and nervous system disorders in lixisenatide-treated patients (36.4% versus 46.5% and 16% versus 24%, respectively). The most commonly reported gastrointestinal disorders were nausea (22.1% in lixisenatide-treated patients versus 22.5% in the liraglutide group), dyspepsia (7.8% versus 16.9%, respectively), diarrhoea (2.6% versus 15.5%), abdominal distension (6.5% versus 12.7%) and vomiting (10.4% versus 7.0%). No SAEs or deaths associated with AEs were reported, while two patients in each group discontinued treatment due to AEs[17].

[Commercial in confidence data removed]

3.3.2 GLP-1 mimetics in combination with basal insulin

Comparative safety data for lixisenatide versus exenatide in combination with basal insulin was derived from the indirect comparison[1]. [Commercial in confidence data removed]

3.4 AWTTC critique

- Lixisenatide is indicated for the treatment of T2DM patients 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[2,3]. In addition to use as a treatment option in patients uncontrolled on basal insulin, the applicant company has suggested that lixisenatide should be placed as a treatment option for patients uncontrolled on two or more oral antidiabetic medications[1]. Current NICE guidance recommends that GLP-1 mimetics, including exenatide twice-daily or prolonged-released formulations and liraglutide, should be considered as a third-line therapy when control of blood glucose remains or becomes inadequate, in specific patient groups and under certain circumstances (see Section 2.1)[7,8]. However, it is unclear if the patient population enrolled in the submitted clinical studies reflects the use of lixisenatide as a third-line therapy[1].
- NICE TA248 recommends the use of exenatide prolonged-release in combination with oral antidiabetic therapy as a treatment option for people with T2DM as described in NICE CG87[10]. No evidence has been provided for lixisenatide versus exenatide prolonged-release in combination with oral antidiabetic therapy[1]. The applicant company states that this formulation of exenatide is not considered a relevant comparator as it has received minimal uptake since its introduction and is typically used in a subgroup of patients requiring assistance to administer their injections[1].
- As part of the evidence provided to support use of lixisenatide in the indication under consideration, the company submission includes comparative evidence of lixisenatide in combination with basal insulin versus exenatide twice-daily[1]. AWMSG has issued a Statement of Advice for exenatide twice-daily in combination with basal insulin (see Section 2.3)[13]. Liraglutide and exenatide prolonged-release are not licensed for use in combination with basil insulin.
- The company submission includes direct comparative evidence of lixisenatide versus exenatide in combination with oral glucose-lowering products

(GetGoal-X)[1,14]. Additionally, as comparative evidence of lixisenatide versus liraglutide, the applicant company has provided a phase II pharmacokinetic study (PDY10931) and an MTC[1,17]. The studies included within the MTC differed with regard to inclusion and exclusion criteria, disease severity, baseline characteristics, concomitant medications and dosing regimens[1]. The applicant company explored the impact of covariates using meta-regression analysis, and state that few of these significantly influenced the outcomes of the MTC. [Commercial in confidence data removed] Due to these differences in methodology and patient population, the findings of the MTC should be interpreted with caution.

- The company submission includes an indirect comparison between lixisenatide and exenatide twice-daily in T2DM patients concurrently receiving basal insulin[1]. While a common approach to the lack of direct head-to-head comparison data, an indirect comparison has inherent limitations. The studies included in the indirect comparison (GetGoal-L and GCWO) differed in several ways, including inclusion criteria, study duration, concomitant medication and body weight[1,19,21]. Additionally, basal insulin doses in study GCWO were increased in order to achieve FPG < 5.6 mmol/l, whilst for GetGoal-L basal insulin was not titrated in order to achieve an FPG target[19,21]. Any conclusions drawn from this indirect comparison should be viewed in light of these limitations.
- Study PDY10931 demonstrated smaller HbA_{1c} reductions from baseline in lixisenatide-treated patients than those in the liraglutide group[17]. However, HbA_{1c} is a measure of average blood glucose levels over the preceding months (see Glossary) and so direct conclusions based on HbA1c data from this 28-day study are limited.
- The CHMP guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus states that a noninferiority margin of 0.3% (3 mmol/mol) is generally considered as acceptable[23]. GetGoal-X utilised a predefined noninferiority margin of 0.4% based on regulatory requirements at the time of study initiation, but the primary endpoint of reduction of HbA_{1c} in the mITT population would still be statistically noninferior should the recommended margin of 0.3% be applied[14,16]. However, CHMP suggested that application of the recommended noninferiority margin in the completer population indicated that lixisenatide may be inferior to exenatide[16]. Further, the reduction in body weight was larger for exenatide-treated patients than for lixisenatide-treated patients. Despite this, CHMP considered that the mean reductions of HbA_{1c} and body weight were of clinical relevance and noted that the lixisenatide group had a lower incidence of nausea and hypoglycaemia[16].
- Several of the studies included as part of the company submission utilise a two-step lixisenatide initiation regimen (including GetGoal-X and GetGoal-L)[1], which is not included as part of the SPC[2,3]. However, the GetGoal-F1 study evaluated the two-step regimen versus the licensed one-step regimen; similar results were obtained in both groups versus placebo[24].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The applicant company has submitted a cost-minimisation analysis (CMA) and cost-utility analysis (CUA) of lixisenatide (Lyxumia®▼) 10 micrograms and 20 micrograms solution for injection administered once daily for the treatment of adults with T2DM 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[1]. Lixisenatide is a GLP-1 agonist, and the company

submission effectively reflects the use of lixisenatide as an alternative to other GLP-1 agonists currently used in Wales (exenatide and liraglutide) within their licensed indications.

For the use of lixisenatide in combination with oral antidiabetic medications, the company considered the comparators to be exenatide twice-daily and liraglutide 1.2mg once-daily. The predominant treatment used in Wales was stated to be liraglutide. The long-acting formulation of exenatide (Bydureon®), which is dosed once-weekly, is not considered by the company as a comparator due to reported low uptake in Wales, and the 1.8mg dose of liraglutide was not considered on the grounds this was not recommended by NICE[11]. The only comparator considered for use in combination with insulin is exenatide twice-daily, as liraglutide does not have a licence for use in this indication. The company stated that treatments outside the GLP-1 agonist class were not likely to be displaced by the introduction of lixisenatide and so were not considered in the economic evaluation.

As a base case analysis, the company presented a CMA. Data from the GetGoal-X study, which demonstrated the noninferiority of lixisenatide versus exenatide in HbA_{1c} reduction at the predefined margin of ≤ 0.4%[14], was used to support the assumption of equivalence in outcomes compared to exenatide in combination with oral antidiabetic medications[1]. A Bucher indirect treatment comparison was used to compare against exenatide in combination with basal insulin, and a Bayesian MTC to support equivalence versus liraglutide in combination with oral antidiabetic medications.

An assessment of cost was performed over a one-year time horizon, but extrapolated to five years, which was stated to be the expected duration of treatment with a GLP-1 agonist[1], based on the assumption used in the economic modelling performed for NICE CG87[7]. In the analysis versus exenatide, costs of medicines and needles are included while other costs, including basal insulin, oral antidiabetic medications and insulin monitoring, are assumed to be equal[1]. In the analysis versus liraglutide, only medicine costs have been compared, as both therapies are administered once-daily. Medicine costs are reported to be based on Monthly Index of Medical Specialities (MIMS) prices[25].

The GetGoal-X trial and indirect comparison show that there are no statistically significant differences between lixisenatide and exenatide on the primary endpoint of HbA_{1c} reduction[1,14]. However, exenatide demonstrated a statistically significant improvement in weight reduction during the GetGoal-X study, [commercial in confidence data removed]. Therefore, the company has also provided a CUA for lixisenatide in the indications considered to take account of differences in outcomes[1]. For this, the commercially-available CORE diabetes model was used.

The CORE model is a Markov-based simulation model that uses the UK Prospective Diabetes Study (UKPDS) outcomes model to estimate the incidence of T2DM complications over time, based on a set of risk equations, including HbA_{1c}, weight, systolic blood pressure and lipid parameters, as well as cardiovascular and all-cause mortality. A time horizon of 50 years was adopted in the analysis performed. Patient baseline characteristics were primarily derived from the GetGoal-X trial[14], for the oral antidiabetic medications combination comparison with exenatide and liraglutide, the GetGoal-L trial[19], for the basal insulin combination comparison with exenatide, and supplemented by Scottish Diabetes Audit, Welsh Health Survey and published estimates. Treatment effect data for risk factors, hypoglycaemia (severe/major, symptomatic, minor), and gastrointestinal AEs (nausea, vomiting and diarrhoea) were entered into the CORE model based on data from the GetGoal-X trial, MTC or indirect comparison.

In all analyses, it was assumed that patients would switch to basal insulin or intensified insulin when HbA_{1c} rose above 8.42%, based on data from a trial of basal-bolus regimens[26]. For the comparison with liraglutide, it was also assumed that lixisenatide patients would switch to liraglutide at one year if they did not achieve a target HbA_{1c} of < 7%, or otherwise would remain on lixisenatide and switch to insulin therapy when HbA_{1c} threshold of 8.42% was exceeded.

A systematic literature review was conducted to derive estimates of T2DM complication utilities and AE disutilities[27]. Healthcare costs associated with T2DM complications and hypoglycaemia were derived from UK literature, NHS reference costs for 2011–2012 or other publications. No costs for AEs were estimated.

GLP-1 agonist and concomitant medicine costs were derived from the British National Formulary (BNF) March 2013[28]. The analysis also captured needle costs and the cost of self monitoring of blood glucose (SMBG) post GLP-1 agonist treatment[1]. Basal insulin weighted costs were based on market share of basal products in the UK.

Scenario and probabilistic sensitivity analyses (PSA) were performed. Scenario analyses consisted of:

- Including only treatment effects where there was a statistically significant difference between treatments shown by the direct or indirect comparison data
- Excluding the disutility associated with patient BMI increase (of 0.061 per unit BMI increase above 25 kg/m^2)
- Using the upper and lower 95% CIs for change in HbA_{1c} from baseline for each comparator
- Setting a lower HbA_{1c} treatment switch threshold value of 8%
- Using a non-sequential approach to the comparison with liraglutide
- Including a disutility for injection burden.

The PSA was performed to account for uncertainty in utility, hypoglycaemia and AE parameters.

4.1.2 Results

The results of the base case analyses using CMA show that lixisenatide is cost saving when compared with both exenatide twice-daily and liraglutide, regardless of indication (Table 5). Savings are driven by the difference in medicine costs, for both comparators, and the cost of needles, in the case of exenatide twice-daily.

Table 5. CMA base case analysis results.

	Lixisenatide costs	Comparison with exenatide twice-daily		Comparison with liraglutide 1.2 mg	
		Exenatide costs	Difference	Liraglutide costs	Difference
Cost per pack*	£54.14	£68.24		£78.48	
Cost per day	£1.93	£2.27		£2.62	
Annual drug costs	£705.75	£830.25	**−£124.50**	£954.84	**−£249.09**
Needle cost per day	£0.09	£0.18		£0.09	
Annual needle costs	£33.73	£67.46	**−£33.73**	£33.73	**£0**
Total annual cost	£739.48	£897.71	**−£158.26**	£988.57	**−£249.09**
Total five-year cost†	£3,697	£4,489	**−£791**	£4,943	**−£1,246**
Plausibility	Assumptions of equivalence in efficacy and safety and similar monitoring and co-medications is not robustly supported by the evidence from the direct and indirect trial evidence used, so CMA case has low plausibility.				

* 28 days for lixisenatide; 30 days for exenatide and liraglutide. Lixisenatide has the same cost per day for the 10 micrograms and 20 micrograms doses.
† Assuming five-year duration of treatment based on GLP-1 agonist duration estimated in the economic model for NICE CG87[7]. Five-year costs not discounted.

For the liraglutide comparison, the results are also presented as a sequence analysis, comparing the costs of a pathway in which patients start with lixisenatide and then switch to liraglutide for the remainder of five years if they fail to reach an HbA_{1c} target of < 7% at 24 weeks, compared to the costs of a pathway in which patients stay on liraglutide for the whole five years, regardless of response. [Commercial in confidence data removed]

The results of the CUA scenario analysis using the CORE model are presented in Table 6. [Commercial in confidence data removed]

[Commercial in confidence data removed]

Table 6. CUA scenario analysis results for the oral antidiabetic medicines and basal insulin combination comparisons.

[Commercial in confidence data removed]

Table 7. Results of CUA scenario analyses.

	Oral antidiabetic medicine combination comparisons						Basal insulin combination comparison			Plausibility
	Lixisenatide versus exenatide twice-daily			Lixisenatide versus liraglutide 1.2 mg			Lixisenatide versus exenatide twice-daily			
	Cost difference	QALY difference	ICER†	Cost difference	QALY difference	ICER†	Cost difference	QALY difference	ICER†	
Statistically significant between treatment effects only*	*	*	*	*	*	*	*	*	*	Not more plausible than base case CUA, but useful scenario
No disutility for BMI change	*	*	*	*	*	*	*	*	*	Less plausible than base case CUA
HbA1c change from baseline for comparator: Lower 95% CrI	*	*	*	*	*	*	*	*	*	Not more plausible than base case CUA but useful for showing uncertainty
HbA1c change from baseline for comparator: Upper 95% CrI	*	*	*	*	*	*	*	*	*	
HbA_{1c} treatment switch threshold of 8%	*	*	*	*	*	*	*	*	*	There is uncertainty over the appropriate threshold in clinical practice. A lower threshold (justified by NICE guidance) could be equally as plausible as the base case value used
Non-sequential comparison with liraglutide	*	*	*	*	*	*	*	*	*	Could be as plausible for clinical practice
Inclusion of injection disutility (disutility of 0.005 for two versus one injection)	*	*	*	*	*	*	*	*	*	Not more plausible but useful scenario analysis
* Commercial in confidence figures removed.										

4.1.3 AWTTC critique

The CMA submitted by the company could be considered invalid as, based on the clinical trial and indirect treatment comparison evidence (see Section 3), the requirement for equivalence in clinical effectiveness and safety outcomes has not been met for lixisenatide versus each comparator.

[Commercial in confidence data removed] As exenatide is administered twice daily, the estimated QALY loss is reduced if a disutility for additional needle injections is included. However, the results versus exenatide in combination with oral antidiabetic medications are sensitive to applying a lower HbA_{1c} treatment switch threshold.

Strengths of the economic evaluation include:

- Direct comparative evidence is used for the comparison versus exenatide in combination with oral antidiabetic medications
- The CORE model used for the CUA is an established model used in previous health technology assessments in the economic evaluation of T2DM treatments.
- The utility estimates and costs associated with T2DM complications included in the model appear reliable.

Limitations of the economic evidence include:

- The CMA presented as the base case lacks validity due to the assumptions of clinical equivalence not being met. Whilst cost savings are estimated, the analysis takes no account of differences in effectiveness and AEs between lixisenatide and the comparators.
- The GetGoal-X trial enrolled patients uncontrolled on metformin only[14], whereas the current use of GLP-1 agonists, as recommended in NICE guidance, is in patients uncontrolled on dual therapy and for use in restricted circumstances in combination with metformin or a sulphonylurea[7,10,11]. The indirect comparisons performed were in patients uncontrolled on one or two oral antidiabetic medications or basal insulin. Hence, it is not clear how generalisable the direct and indirect trial evidence is to the specific population of patients uncontrolled on two other oral antidiabetic medications for whom lixisenatide could be expected to be prescribed in practice.
- There were several sources of heterogeneity in both the MTC, which compared lixisenatide versus liraglutide in combination with oral antidiabetic medications, and the Bucher indirect comparison, which compared lixisenatide versus exenatide in combination with basal insulin. These included: differences in study selection criteria, baseline HbA_{1c}, differences in study follow-up and in the concomitant medications used (see Section 3.4).
- [Commercial in confidence data removed]
- The CUA results are sensitive to the HbA_{1c} treatment switch threshold assumed. The HbA_{1c} treatment switch threshold recommended by NICE guidance when considering GLP-1 agonists is ≥ 7.5% for patients who have failed on metformin and sulfonylurea[7]. Hence, the use of a treatment switch threshold of 8.42% in the economic analysis may be too high for the use of GLP-1 agonists in combination with oral antidiabetic medications in clinical practice, [commercial in confidence data removed].
- The company did not consider exenatide modified-release as a possible comparator, explaining that its uptake in Wales has been low.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of lixisenatide within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data from the National Diabetes Audit for the years 2010–2011[29,30], the applicant company estimates that the number of patients with T2DM in Wales in 2013 is 154,801[1]. The company also estimates that 6,131 patients in Wales received GLP-1 agonist therapy in the year to January 2013, based on IMS cash sales data, and that this number is forecasted to increase to 7000 by the end of 2013, and to increase by 1000 patients per year thereafter. The company forecasts that lixisenatide market share will be 13% by the end of 2013 and will rise to 33% by 2017. Hence, the number of patients treated with lixisenatide is estimated to be 910 in 2013, rising to 3,630 in 2017.

5.1.2 Results

Assuming that 40% of lixisenatide recipients will displace liraglutide 1.2 mg, and 60% will displace exenatide twice-daily, the company anticipates an overall net cost saving from switching to lixisenatide from the two comparators[1]. This saving is estimated to be over £177,000 in 2013 and to rise to over £700,000 in 2017. The results of this base case analysis are presented in Table 8.

The company also reports the results of sensitivity analyses around the estimated number of patients to be treated with lixisenatide (−50% to +200% of the base case estimates) and the relative displacement of exenatide twice-daily and liraglutide. The results show that lixisenatide remains cost saving across the ranges explored with the estimated saving ranging from £858,376 to £5.41 million over the five years.

Table 8. Company-reported base case costs with the use of lixisenatide in Wales.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication(s) covered in this submission)	7000	8000	9000	10,000	11,000
Uptake (%)	13%	18%	23%	28%	33%
Treated patients	910	1,440	2,070	2,800	3,630
Net costs versus weighted average of comparators					
Net cost per patient (drug and needles costs)	−£194.57	−£194.57	−£194.57	−£194.57	−£194.57
Overall net cost	**−£177,060**	**−£280,183**	**−£402,763**	**−£544,801**	**−£706,295**

5.1.3 AWTTC critique

- The company has made reasonable effort to characterise the epidemiology of T2DM in Wales, using Welsh-specific data.
- The validity of the anticipated savings is dependent on the validity of the usage levels of the different comparators and the percentage switch from each of the comparators to lixisenatide.

5.2 Table of comparative unit costs

Examples of acquisition costs for lixisenatide and its comparators are shown in Table 9. See NICE CG87 (T2DM management)[7], and Technology Appraisals 203 (liraglutide)[11] and 248 (exenatide modified-release)[10] for recommended use and place in therapy.

Table 9. Examples of annual acquisition costs for GLP-1 receptor agonists.

Drug	Example dose*	Annual cost per patient†
Lixisenatide (Lyxumia®▼) Solution for injection, 10 micrograms and 20 micrograms	Starting dose: 10 micrograms once-daily for 14 days. Maintenance dose: 20 micrograms once-daily from Day 15.	**£706**
Liraglutide (Victoza®) 1.2 mg dose Solution for injection, 6 mg/ml	Maintenance dose: 1.2 mg once-daily	**£955**
Liraglutide (Victoza®) 1.8 mg dose Solution for injection, 6 mg/ml	Maintenance dose: 1.8 mg once-daily	**£1,432**
Exenatide (Byetta®) Solution for injection, 5 micrograms and 10 micrograms	Maintenance dose: 10 micrograms twice-daily	**£830**
Exenatide (Bydureon®) Powder and solvent for prolonged-release suspension for injection, 2 mg	Dose: 2 mg once-weekly	**£954**

*Doses based on SPCs[2,3,15,18,31] and BNF[28].
† Costs are based on current BNF list prices as of August 2013[28], with the exception of the cost of lixisenatide which is based on the company submission that states a flat price for the 10 microgram and 20 microgram doses. The cost of needles for administration is not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant SPCs for full dosing details[2,3,15,18,31].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, lixisenatide (Lyxumia®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that lixisenatide (Lyxumia®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted an ongoing study that is likely to be available within 6–12 months:

- NCT01147250: Evaluation of cardiovascular outcomes in patients with type 2 diabetes after acute coronary syndrome during treatment with lixisenatide (ELIXA)[32].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 29 August 2013 and 30 August 2013
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Glycosylated haemoglobin (HbA_{1c})

This reflects the blood glucose level of a patient, where a higher HbA_{1c} level means more glucose has been present in the blood in the preceding few months[33,34]. Previously, HbA_{1c} results were reported as a percentage; however, from October 2011, laboratories in the UK switched to reporting results using new HbA_{1c} units, mmol/mol[33] (see Table 10).

Table 10. Comparison of HbA_{1c} results[33].

HbA_{1c} (%)	HbA_{1c} (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75

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