# Type 2 diabetes: lixisenatide

Evidence summary

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nice.org.uk/guidance/esnm26

This advice replaces ESNM10.

## Key points from the evidence

The content of this evidence summary was up-to-date in September 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

*Summary*

The glucagon-like peptide-1 (GLP-1) mimetic lixisenatide is more effective than placebo in reducing glycated haemoglobin ($HbA_{1c}$) in people with type 2 diabetes who are receiving oral antidiabetic drugs or basal insulin. Non-inferiority to exenatide has not been shown robustly for this outcome. There are no published data relating to patient-oriented outcomes or long-term safety.

| Effectiveness | Safety |
|---|---|
| In people receiving metformin or pioglitazone or both (3 RCTs, 24 weeks):<br><br>• 0.8–0.9% point reduction in $HbA_{1c}$ from baseline; 0.4–0.6% point greater reduction than placebo.<br><br>• Non-inferiority to exenatide not shown robustly.<br><br>• Reduction in body weight from baseline but no difference in weight change compared with placebo; less weight reduction than with exenatide.<br><br>In people receiving basal insulin with or without metformin (2 RCTs, 24 weeks):<br><br>• 0.7% point reduction in $HbA_{1c}$ from baseline; 0.3% point greater reduction than placebo.<br><br>• Weight reduction or less weight increase compared with placebo. | • GLP-1 mimetics have been associated with a risk of developing acute pancreatitis. |
| **Patient factors** | **Resource implications** |
| • Once-daily administration by injection.<br><br>• Nausea, vomiting, diarrhoea and headache are very common (frequency 1 or more in 10), as is hypoglycaemia when lixisenatide is used in combination with a sulfonylurea and/or a basal insulin.<br><br>• When compared with exenatide, fewer people had nausea and symptomatic hypoglycaemia. | • Annual acquisition cost £705.75; this is 15–26% less than other GLP-1 mimetics. |

## *Key points*

Lixisenatide is a GLP-1 mimetic licensed for use in combination with oral antidiabetic drugs and/or basal insulin for treating type 2 diabetes in adults whose blood glucose is not adequately controlled on these treatments alone. It is administered by subcutaneous injection once daily.

NICE published an evidence summary on lixisenatide for type 2 diabetes in January 2013 (ESNM10). However, studies that are more applicable to the UK population and to lixisenatide's

licensed indications have been published in full since that summary was prepared. These have been reviewed in this evidence summary, which now updates and replaces the earlier evidence summary on lixisenatide.

Lixisenatide in combination with oral therapies has been investigated in 3 randomised controlled trials (RCTs) that have been published in full:

- GetGoal-P (Pinget et al. 2013) compared lixisenatide with placebo in people whose diabetes was poorly controlled on pioglitazone, with or without metformin.

- GetGoal-M (Ahrén et al. 2013) compared lixisenatide with placebo in people whose diabetes was poorly controlled on metformin monotherapy.

- GetGoal-X (Rosenstock et al. 2013) compared lixisenatide with exenatide in people on metformin monotherapy.

GetGoal-P and GetGoal-M found that lixisenatide was more effective than placebo with regard to their primary outcome of reduction in $HbA_{1c}$ from baseline. However, the 0.8–0.9 percentage point mean reductions from baseline in the lixisenatide groups were slightly less than the 1.0 percentage point (11 mmol/mol) reduction specified in NICE guidance as a criterion for continuing treatment with exenatide or liraglutide in triple or dual therapy beyond 6 months, and the mean difference from placebo was about half of that (see the Introduction for details of NICE guidance).

GetGoal-M and GetGoal-P both found a statistically significant reduction in fasting plasma glucose with lixisenatide compared with placebo, and GetGoal-M found a statistically significant reduction in 2-hour post-prandial plasma glucose (this end point was not reported in GetGoal-P). There was no statistically significant effect from lixisenatide on body weight compared with placebo in either study. However, the European Medicines Agency (EMA) concluded that the effect of lixisenatide on body weight was of clear clinical relevance and advantageous compared with the increase in weight with some other therapeutic options.

GetGoal-X concluded that lixisenatide was non-inferior to exenatide with regard to the primary outcome of reduction in $HbA_{1c}$ from baseline. However, the EMA concluded that non-inferiority to exenatide had not been shown robustly (see the sections on Evidence strengths and limitations and Likely place in therapy for more details). There was no statistically significant difference in fasting plasma glucose between lixisenatide and exenatide. Exenatide produced a statistically significantly greater mean reduction in bodyweight. Statistically significantly fewer people receiving lixisenatide reported nausea or symptomatic hypoglycaemia compared with those receiving exenatide.

Lixisenatide in combination with insulin has been investigated in 2 RCTs relevant to the UK population and that have been published in full:

- GetGoal-L (Riddle et al. 2013a) compared lixisenatide with placebo in people whose diabetes was poorly controlled on basal insulin, with or without metformin.

- GetGoal-Duo1 (Riddle et al. 2013b) compared lixisenatide with placebo in people whose diabetes was poorly controlled on recently initiated insulin glargine, plus oral agents.

Lixisenatide was more effective than placebo for the primary outcome of reduction in $HbA_{1c}$ from baseline, producing mean reductions of 0.7 percentage points and mean differences from placebo of 0.3 percentage points in both studies.

Gastrointestinal adverse effects are often reported with GLP-1 mimetics. The summary of product characteristics (SPC) states that the most frequently reported adverse reactions during clinical studies of lixisenatide were nausea, vomiting and diarrhoea (very common: frequency 1 or more in 10). These reactions were mostly mild and transient. In addition, headache was also very common, as was hypoglycaemia when lixisenatide was used in combination with a sulfonylurea and/or a basal insulin. The SPC notes that GLP-1 mimetics have been associated with a risk of developing acute pancreatitis.

Lixisenatide has a lower acquisition cost than the other GLP-1 mimetics currently available.

The place in therapy of exenatide and liraglutide, the other 2 GLP-1 mimetics currently available in the UK, is described in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87), Liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal guidance 203) and Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (NICE technology appraisal guidance 248). Exenatide, liraglutide and lixisenatide will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

Local decision makers will need to consider the evidence for lixisenatide in type 2 diabetes alongside that for other GLP-1 mimetics, taking into account current NICE guidance, differences in individual patient factors and the acquisition costs of the different products.

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**Key evidence**

Pinget M, Goldenberg R, Niemoeller E et al. (2013) Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes, Obesity and Metabolism doi: 10.1111/dom.12121

Riddle MC, Aronson R, Home P et al. (2013) Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care doi: 10.2337/dc12-2454

Rosenstock J, Raccah D, Koranyi L et al. (2013) Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care doi: 10.2337/dc12-2709

## About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Relevance to NICE guidance programmes

Lixisenatide in type 2 diabetes will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

## Introduction

The NICE clinical guideline on type 2 diabetes states that the management of type 2 diabetes is complex. It involves an individualised, multifactorial approach that addresses blood pressure, blood lipids and lifestyle issues, as well as blood glucose. As the MeReC Bulletin on type 2 diabetes discusses, controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The NICE clinical guideline on type 2 diabetes recommends that people should be involved in setting their individualised $HbA_{1c}$ target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to $HbA_{1c}$ levels below 48 mmol/mol (6.5%) should be avoided.

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The natural hormone glucagon-like peptide-1 (GLP-1) acts by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake. In addition to lixisenatide, there are 2 other GLP-1 mimetics currently licensed and available in the UK: exenatide and liraglutide. All are administered by injection.

The NICE clinical guideline on type 2 diabetes, which is being updated, advises that consideration should be given to adding exenatide as third-line therapy in triple therapy in addition to metformin and a sulfonylurea when control of blood glucose remains or becomes inadequate (HbA$_{1c}$ 59 mmol/mol [7.5%] or greater, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) of 35.0 kg/m$^2$ or more 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 less than 35.0 kg/m$^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

The guideline also advises that exenatide should be continued only if the person has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0 percentage point] in HbA$_{1c}$ and a weight loss of at least 3% of initial body weight at 6 months).

The NICE technology appraisal on liraglutide for the treatment of type 2 diabetes mellitus recommends liraglutide 1.2 mg daily in triple therapy (in combination with metformin and a sulfonylurea, or metformin and a glitazone) as an option in the same clinical situations and with the same criteria for continuation as for exenatide in the NICE clinical guideline on type 2 diabetes.

The NICE technology appraisal on liraglutide recommends liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulfonylurea) as an option only if:

- the person is intolerant of either metformin **or** a sulfonylurea, or treatment with metformin **or** a sulfonylurea is contraindicated, **and**

- the person is intolerant of glitazones **and** dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with glitazones **and** DPP-4 inhibitors is contraindicated.

It also recommends that treatment with liraglutide in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 11 mmol/mol [1.0 percentage point] in HbA$_{1c}$ at 6 months).

The NICE technology appraisal on exenatide prolonged-release suspension for the treatment of type 2 diabetes recommends prolonged-release exenatide in triple therapy (in combination with metformin and a sulfonylurea, or metformin and a glitazone) as an option in the same clinical situations and with the same criteria for continuation as for exenatide in the NICE clinical guideline on type 2 diabetes. It also recommends prolonged-release exenatide in dual therapy (in combination with metformin or a sulfonylurea) as an option in the same clinical situations and with the same criteria for continuation as for liraglutide in dual therapy regimens in the NICE technology appraisal on liraglutide.

Lixisenatide in type 2 diabetes will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. The publication date for this guideline is to be confirmed

See the MeReC Bulletin on type 2 diabetes, the type 2 diabetes key therapeutic topic and the NICE pathway on diabetes for more information. See also the Clinical Knowledge Summary on type 2 diabetes for a general overview of prescribing considerations.

## Product overview

### Drug action

Lixisenatide is a glucagon-like peptide-1 (GLP-1) mimetic.

### Therapeutic indication

The summary of product characteristics states that lixisenatide (Lyxumia) is licensed for treating 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.

### Course and cost

Lixisenatide is administered as a once-daily subcutaneous injection using a fixed-dose pen device. The summary of product characteristics states that dosing is initiated at 10 micrograms once daily for 14 days, followed by a maintenance dose of 20 micrograms once daily thereafter. The dose should be administered within the hour before the first meal of the day or the evening meal.

A 2-pen pack (28 days' supply) costs £54.14, with flat pricing across initiation and maintenance doses (cost taken from MIMS July 2013 and excluding VAT).

# Evidence review

This evidence summary updates and replaces an earlier evidence summary on lixisenatide, which was published in January 2013 (ESNM10). That summary was based on the 2 randomised controlled trials (RCTs) of lixisenatide that had been published when lixisenatide was marketed: GetGoal-Mono (Fonseca et al. 2012) and GetGoal-L-Asia (Seino et al. 2012). However, these 2 RCTs have not been prioritised for inclusion in this evidence summary. GetGoal-Mono investigated lixisenatide as monotherapy, which does not reflect the UK licensed indication. GetGoal-L-Asia investigated lixisenatide in combination with basal insulin with or without a sulfonylurea, but was conducted in an Asian population, which does not reflect the majority of the UK population. The GetGoal-L-Asia authors noted that incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) mimetics, are particularly effective in people of Asian or Japanese family origin because of the underlying pathophysiology of diabetes in these groups of people.

This evidence summary is based on 3 RCTs of lixisenatide in people with type 2 diabetes, which have been published in full since January 2013:

- GetGoal-P (Pinget et al. 2013) compared lixisenatide with placebo in people whose diabetes was poorly controlled on pioglitazone, with or without metformin.

- GetGoal-X (Rosenstock et al. 2013) compared lixisenatide with exenatide in people on metformin monotherapy.

- GetGoal-L (Riddle et al. 2013a) compared lixisenatide with placebo in people whose diabetes was poorly controlled on basal insulin, with or without metformin.

In addition, 2 other RCTs are briefly discussed: GetGoal-M (Ahrén et al. 2013), which compared lixisenatide with placebo in people whose diabetes was poorly controlled on metformin monotherapy; and GetGoal-Duo1 (Riddle et al. 2013b), which compared lixisenatide with placebo in people whose diabetes was poorly controlled on recently initiated insulin glargine, plus oral agents.

Two other placebo-controlled RCTs in the GetGoal programme have been completed but have not yet been published in full: GetGoal-F1 (lixisenatide in combination with metformin) and GetGoal-S (lixisenatide in combination with a sulfonylurea, with or without metformin). In accordance with the integrated process statement for evidence summaries: new medicines, they have not been included in this evidence summary.

In GetGoal-P, GetGoal-X and GetGoal-L, HbA$_{1c}$ results were reported only in percentages and these have not been converted to mmol/mol in this evidence summary. The Diabetes UK website indicates that a 0.5 percentage point difference in HbA$_{1c}$ is equivalent to a difference of about 5.5 mmol/mol, and a 1 percentage point difference is equivalent to a difference of about 11 mmol/mol. Note that these are rounded equivalents.

GetGoal-P (Pinget et al. 2013)

- Design: a double-blind RCT conducted in 150 centres in 13 countries in Europe, India and North and South America. The study included a 24-week main study and a variable double-blind extension period that continued until the last patient had completed a total of 76 weeks' treatment. Allocation was concealed.

- Population: 484 adults, mean age 56 years, with type 2 diabetes of at least 1 year's duration (mean 8.1 years), HbA$_{1c}$ 7.0% to 10.0% (mean 8.1%) and fasting plasma glucose (FPG) 13.9 mmol/l or less (mean 9.1 mmol/l), who had been treated with a stable dose of pioglitazone 30 mg/day or more (median dose 30 mg) for at least 3 months (mean 1.8 years). In addition, 81% of patients were treated with metformin 1.5 g/day or more (median dose 2 g/day); the median duration of metformin treatment was 3.4 years. At trial entry, 68% of patients had a body mass index (BMI) of 30 kg/m$^2$ or greater (median 34 kg/m$^2$).

- Intervention and comparison: patients were randomised 2:1 to lixisenatide or placebo, administered no longer than 1 hour before breakfast. Patients randomised to lixisenatide received 10 micrograms once daily for 1 week, then 15 micrograms once daily for 1 week, then 20 micrograms once daily, if tolerated. If the target dose of lixisenatide could not be tolerated, the dose could be reduced. Patients continued on their established doses of pioglitazone and metformin.

- Outcome: the primary efficacy outcome was the absolute change in HbA$_{1c}$ from baseline to week 24 for the modified intention-to-treat population (all randomised patients who received at least 1 dose of study treatment and had a baseline assessment and at least 1 post-baseline assessment). This was analysed using analysis of covariance (ANCOVA), stratified by screening level HbA$_{1c}$ and whether or not the person was taking metformin. The last observation carried forward (LOCF) method was used to handle missing data by taking the last available HbA$_{1c}$ as the HbA$_{1c}$ value at week 24: 35 patients randomised to lixisenatide (10.8%) and 24 patients randomised to placebo (14.9%) discontinued treatment prematurely. In addition, 74% of patients randomised to lixisenatide and 68% of those randomised to placebo completed the extension period. Secondary efficacy outcomes included the percentage of patients with an HbA$_{1c}$ of less than 7.0% and changes in FPG and body weight from baseline.

Table 1 Summary of GetGoal-P (Pinget et al. 2013)

|  | Placebo | Lixisenatide | Analysis (lixisenatide versus placebo) |
|---|---|---|---|
| **Efficacy[a]** | n=148 | n=308 | |
| Primary outcome: LS mean change in $HbA_{1c}$ from baseline to week 24[b] | −0.34% points from baseline of 8.1% | −0.9% points from baseline of 8.1% | LS mean change difference −0.56% points, 95% CI −0.73 to −0.39, p<0.0001 |
| Selected secondary outcomes: | | | |
| Patients with $HbA_{1c}$ of less than 7.0% at week 24[b] | 26.4% | 52.3% | p<0.0001 |
| LS mean change in FPG from baseline to week 24[b] | −0.32 mmol/l from baseline of 9.1 mmol/l | −1.16 mmol/l from baseline of 9.1 mmol/l | LS mean change difference −0.84 mmol/l, 95% CI −1.21 to −0.47, p<0.0001 |
| LS mean change in body weight from baseline to week 24[b] | +0.2 kg from baseline of 96.7 kg | −0.2 kg from baseline of 92.9 kg | LS mean change difference −0.41 kg, 95% CI −1.03 to 0.20, p=0.19 (not statistically significant) |
| **Safety[c]** | n=161 | n=323 | |
| Serious adverse events | 1.9% (3/161) | 2.5% (8/323) | p value not stated |
| Death | 0.6% (1/161) | 0 | p value not stated |
| Adverse events leading to discontinuation | 5.0% (8/161) | 6.5% (21/323) | p value not stated |
| Gastrointestinal disorders | 28.6% (46/161) | 36.5% (118/323) | p value not stated |
| Symptomatic hypoglycaemia[d] | 1.2% (2/161) | 3.4% (11/323) | p value not stated |
| Severe symptomatic hypoglycaemia[e] | 0 | 0 | |

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least square.

[a] Modified intention-to-treat population: all patients who received at least 1 dose of study treatment and had baseline assessment and at least 1 post-baseline assessment of any primary or secondary efficacy variable.

[b] ANCOVA analysis with last observation carried forward.

[c] All patients who received at least 1 dose of study treatment: results to week 24.

[d] Symptoms of hypoglycaemia with blood glucose less than 3.3 mmol/l and/or prompt recovery with carbohydrate.

[e] Symptoms of hypoglycaemia requiring the assistance of another person, with blood glucose less than 2.0 mmol/l or prompt recovery with carbohydrate.

GetGoal-X (**Rosenstock et al. 2013**)

- Design: a 24-week, open-label, non-inferiority study conducted in 122 centres in 18 countries in Europe and North and South America. Allocation was concealed.

- Population: 639 adults, aged 21 to 84 years (mean 57 years), with type 2 diabetes (mean duration 6.8 years), $HbA_{1c}$ 7.0% to 10.0% (mean 8.02%) and FPG 13.9 mmol/l or less (mean 9.7 mmol/l), who had been receiving metformin 1.5 g per day or more (mean daily dose 2 g). Mean BMI was 33.6 kg/m$^2$. Patients had received no glucose-lowering agents other than metformin in the preceding 3 months.

- Intervention and comparison: patients were randomised to receive lixisenatide (10 micrograms once daily for 1 week, then 15 micrograms once daily for 1 week, then 20 micrograms once daily) or exenatide (5 micrograms twice daily for 4 weeks and then 10 micrograms twice daily). All treatments were administered no longer than 1 hour before breakfast (lixisenatide and exenatide) or the evening meal (exenatide).

- Outcome: the primary efficacy outcome was the change in $HbA_{1c}$ from baseline to week 24 for the modified intention-to-treat population (all randomised patients who received at least 1 dose of study treatment and had a baseline assessment and at least 1 post-baseline assessment). The pre-specified non-inferiority criterion was 0.4% or less, as recommended by regulatory guidelines when the study was designed. This was analysed using ANCOVA, with the treatment group, screening strata for $HbA_{1c}$ and BMI, and country as fixed effects, and with baseline $HbA_{1c}$ as a covariate. The LOCF method was used to handle missing data: 41 patients randomised to lixisenatide (12.9%) and 45 patients randomised to exenatide (14.2%) discontinued treatment prematurely. Secondary efficacy outcomes included the percentage of

patients with an HbA$_{1c}$ less than 7.0% and changes in FPG and body weight from baseline to week 24.

Table 2 Summary of GetGoal-X(Rosenstock et al. 2013)

|  | Exenatide | Lixisenatide | Analysis (lixisenatide versus exenatide) |
|---|---|---|---|
| **Efficacy**[a] | n=315 | n=315 |  |
| Primary outcome: LS mean change in HbA$_{1c}$ from baseline to week 24[b] | −0.96% points from baseline of 7.96% | −0.79% points from baseline of 7.97% | LS mean change difference 0.17% points, 95% CI 0.033 to 0.297 |
| Selected secondary outcomes: | | | |
| Patients with HbA$_{1c}$ of less than 7.0% at week 24[b] | 49.8% | 48.5% | p value not stated |
| LS mean change in FPG from baseline to week 24[b] | −1.45 mmol/l from baseline of 9.7 mmol/l | −1.22 mmol/l from baseline of 9.7 mmol/l | LS mean change difference 0.23 mmol/l, 95% CI −0.052 to 0.522 |
| LS mean change in body weight from baseline to week 24[b] | −3.98 kg from baseline of 96.7 kg | −2.96 kg from baseline of 94.5 kg | LS mean change difference 1.02 kg, 95% CI 0.456 to 1.581 |
| **Safety**[c] | n=316 | n=318 |  |
| Serious adverse events | 2.2% (7/316) | 2.8% (9/318) | p value not stated |
| Death | 0.3% (1/316) | 0.3% (1/318) | p value not stated |
| Adverse events leading to discontinuation | 13.0% (41/316) | 10.4% (33/318) | p value not stated |
| Gastrointestinal disorders | 50.6% (160/316) | 43.1% (137/318) | p value not stated |
| Symptomatic hypoglycaemia[d] | 7.9% (25/316, 48 events) | 2.5% (8/318, 8 events) | p<0.05 |
| Severe symptomatic hypoglycaemia[e] | 0 | 0 |  |

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least square.

[a] Modified intention-to-treat population: all patients who received at least 1 dose of study treatment and had baseline assessment and at least 1 post-baseline assessment of any primary or secondary efficacy variable.

[b] ANCOVA analysis with last observation carried forward.

[c] All patients who received at least 1 dose of study treatment.

[d] Symptoms of hypoglycaemia with blood glucose less than 3.3 mmol/l and/or prompt recovery with carbohydrate.

[e] Symptoms of hypoglycaemia requiring the assistance of another person, with blood glucose less than 2.0 mmol/l or prompt recovery with carbohydrate.

GetGoal-L **(Riddle et al. 2013a)**

- Design: a 24-week, double-blind RCT conducted in 111 centres in 15 countries in Europe, North and South America, Egypt, India and South Korea. Allocation was concealed.

- Population: 495 adults, aged 29 to 81 years (mean 57 years), with type 2 diabetes of at least 1 year's duration (mean 12.5 years), $HbA_{1c}$ 7.0% to 10.0% (mean 8.4%) and FPG 13.9 mmol/l or less (mean 8.1 mmol/l), who had been treated with a stable dose of basal insulin (at least 30 units per day, median 55 units) for at least 2 months (mean 3.1 years): 50% of patients were receiving insulin glargine, 40% were receiving NPH insulin and the remainder were receiving insulin detemir. At trial entry, 79% of patients were treated with metformin 1.5 g/day or more (mean dose 2 g/day). At trial entry, 60% of patients had a BMI of 30 kg/m$^2$ or greater (mean 32 kg/m$^2$).

- Intervention and comparison: patients were randomised 2:1 to lixisenatide or placebo, administered no longer than 1 hour before breakfast. Patients randomised to lixisenatide received 10 micrograms once daily for 1 week, then 15 micrograms once daily for 1 week, then 20 micrograms once daily, if tolerated. Patients continued on their established dose of metformin, if taking it at study entry. The basal insulin dose was to remain stable (±20%) throughout the study, but if the patient's $HbA_{1c}$ was 7.5% or less at pre-entry screening, the dose was reduced by 20% and then progressively increased back to the previous dose between weeks 4 and 12. After week 12, no dose adjustments were permitted except reductions in response to hypoglycaemia.

- Outcome: the primary efficacy outcome was the change in $HbA_{1c}$ from baseline to week 24 for the modified intention-to-treat population (all randomised patients who received at least 1 dose of study treatment and had a baseline assessment and at least 1 post-baseline

assessment). This was analysed using ANCOVA, with the treatment group, screening strata for HbA$_{1c}$ and metformin use, and country as fixed effects, and with baseline HbA$_{1c}$ as a covariate. The LOCF method was used to handle missing data: 53 patients randomised to lixisenatide (16.1%) and 20 patients randomised to placebo (12.0%) discontinued treatment prematurely. Secondary efficacy outcomes included the percentage of patients with an HbA$_{1c}$ of less than 7.0% and changes in FPG and body weight from baseline to week 24.

Table 3 Summary of GetGoal-L (Riddle et al. 2013a)

| | Placebo | Lixisenatide | Analysis (lixisenatide versus placebo) |
|---|---|---|---|
| Efficacy[a] | n=166 | n=327 | |
| Primary outcome: LS mean change in HbA$_{1c}$ from baseline to week 24[b] | −0.4% points from baseline of 8.4% | −0.7% points from baseline of 8.4% | LS mean change difference −0.4% points, 95% CI −0.6 to −0.2, p<0.0002 |
| Selected secondary outcomes: | | | |
| Patients with HbA$_{1c}$ of less than 7.0% at week 24[b] | 12.0% | 28.3% | p<0.0001 |
| LS mean change in FPG from baseline to week 24[b] | −0.6 mmol/l from baseline of 8.0 mmol/l | −0.6 mmol/l from baseline of 8.1 mmol/l | LS mean change difference −0.1 mmol/l, 95% CI −0.6 to 0.4, p=0.76 (not statistically significant) |
| LS mean change in PPG from baseline to week 24[b] | −1.7 mmol/l from baseline of 15.9 mmol/l | −5.5 mmol/l from baseline of 16.4 mmol/l | LS mean change difference −3.8 mmol/l, 95% CI −4.7 to −2.9, p<0.0001 |
| LS mean change in body weight from baseline to week 24[b] | −0.5 kg from baseline of 89 kg | −1.8 kg from baseline of 87 kg | LS mean change difference −1.3 kg, 95% CI −1.8 to −0.7, p<0.0001 |
| Safety[d] | n=167 | n=328 | |
| Serious adverse events | 4.2% (7/167) | 3.7% (12/328) | p value not stated |
| Death | 0 | 0.3% (1/328) | p value not stated |

| Adverse events leading to discontinuation | 4.8% (8/167) | 7.6% (25/328) | p value not stated |
|---|---|---|---|
| Gastrointestinal disorders | 20.4% (34/167) | 40.2% (132/328) | p value not stated |
| Symptomatic hypoglycaemia[e] | 21.6% (36/167, 132 events) | 27.7% (91/328, 309 events) | p value not stated |
| Severe symptomatic hypoglycaemia[f] | 0 | 1.2% (4/328, 4 events) | p value not stated |

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least square; PPG, post-prandial plasma glucose.

[a] Modified intention-to-treat population: all patients who received at least 1 dose of study treatment and had baseline assessment and at least 1 post-baseline assessment of any primary or secondary efficacy variable.

[b] ANCOVA analysis with last observation carried forward.

[c] 2-hour PPG levels after a standardised liquid breakfast meal.

[d] All patients who received at least 1 dose of study treatment.

[e] Symptoms of hypoglycaemia with blood glucose less than 3.3 mmol/l or prompt recovery with carbohydrate.

[f] Symptoms of hypoglycaemia requiring the assistance of another person, with blood glucose less than 2.0 mmol/l or prompt recovery with carbohydrate.

## Clinical effectiveness

### Lixisenatide in combination with oral therapy

GetGoal-P found that lixisenatide was statistically significantly superior to placebo after 24 weeks of treatment in terms of $HbA_{1c}$ reduction from baseline in patients treated with pioglitazone. Most but not all patients were also taking metformin, and the ANCOVA method of analysis would have ensured that the results were adjusted for this variable. However, the use of the LOCF method for handling missing data is a potential source of bias (see Evidence strengths and limitations for more information).

Lixisenatide was also compared with placebo in GetGoal-M (Ahrén et al. 2013). This had a very similar design and method of analysis to GetGoal-P, except that it also compared morning and

evening administration of lixisenatide. It included 680 people with HbA$_{1c}$ 7% to 10% who were taking metformin monotherapy (mean daily dose, 2 g). GetGoal-M found a similar least squares mean reduction in HbA$_{1c}$ from baseline after 24 weeks in the lixisenatide group as in GetGoal-P. Administration of lixisenatide in the morning produced a reduction of 0.9 percentage points (9.8 mmol/mol), a 0.5 percentage point (5.5 mmol/mol) greater reduction than placebo (p<0.0001). Administration of lixisenatide in the evening produced a reduction of 0.8 percentage points (8.7 mmol/mol), a 0.4 percentage point (4.4 mmol/mol) greater reduction than placebo (p<0.0001). GetGoal-M and GetGoal-P both found a statistically significant reduction in fasting plasma glucose with lixisenatide compared with placebo. GetGoal-M found a reduction from baseline in 2-hour post-prandial plasma glucose in the lixisenatide morning group (least squares mean reduction 5.9 mmol/l, a 4.5 mmol/l greater reduction than with placebo, p<0.0001); this end point was not reported in GetGoal-P. There was no statistically significant effect from lixisenatide on body weight compared with placebo in either study.

GetGoal-X found that lixisenatide was non-inferior to exenatide for the primary outcome of reduction in HbA$_{1c}$ from baseline. However, in its public assessment report for lixisenatide (Lyxumia), the European Medicines Agency (EMA) concluded that non-inferiority to exenatide had not been shown robustly (see Evidence strengths and limitations for more information). Exenatide produced a statistically significantly greater mean reduction in bodyweight.

## Lixisenatide in combination with insulin therapy

GetGoal-L found that lixisenatide was statistically significantly superior to placebo after 24 weeks of treatment in terms of HbA$_{1c}$ reduction from baseline in patients established on treatment with basal insulin. Most but not all patients were also taking metformin, and the ANCOVA method of analysis would have ensured that the results were adjusted for this variable. However, the use of the LOCF method for handling missing data is a potential source of bias (see Evidence strengths and limitations for more information).

Lixisenatide was also compared with placebo in conjunction with insulin in GetGoal-Duo1 (Riddle et al. 2013b). This double-blind, multi-national, multicentre RCT recruited 898 adults with type 2 diabetes and HbA$_{1c}$ 7% to 10% despite treatment with metformin alone or in combination with a sulfonylurea, glinide or glitazone. Patients were started on insulin glargine, the dose of which was titrated upwards over 12 weeks (patients continued on metformin and, if used previously, a glitazone). After this period, the 446 patients whose HbA$_{1c}$ remained in the range of 7% to 9% and whose fasting plasma glucose was 7.8 mmol/l or less were randomised to lixisenatide or placebo for 24 weeks, while adjustment of the insulin glargine dose continued. Lixisenatide was titrated up to 20 micrograms daily in a 2-step process, the same as in GetGoal-L.

Introduction of insulin glargine reduced mean $HbA_{1c}$ levels from 8.6% (70 mmol/mol) to 7.6% (60 mmol/mol) at 12 weeks. After 24 weeks of treatment with lixisenatide or placebo (or LOCF), the least squares mean reduction in $HbA_{1c}$ was 0.7 percentage points in the lixisenatide group and 0.4 percentage points in the placebo group (least squares mean difference −0.3 percentage points, 95% confidence interval −0.5 to −0.2, $p<0.0001$). More patients receiving oral therapy, insulin glargine and lixisenatide (56%) had an $HbA_{1c}$ less than 7.0% (53 mmol/mol) compared with those receiving oral therapy, insulin glargine and placebo (39%, $p=0.0001$).

Neither GetGoal-L nor GetGoal-Duo1 found a statistically significant reduction in fasting plasma glucose with lixisenatide compared with placebo, but both studies found a reduction in 2-hour post-prandial plasma glucose compared with placebo (in GetGoal-Duo 1 lixisenatide produced a 3.2 mmol/l greater reduction in least squares mean reduction from baseline compared with placebo, $p<0.0001$). In GetGoal-L, body weight reduced in both the lixisenatide and placebo groups, but to a statistically significantly greater extent in the lixisenatide group (difference −1.3 kg, $p<0.0001$). In GetGoal-Duo1, body weight increased in both study groups, although to a statistically significantly lesser extent in the lixisenatide group (+0.3 kg compared with +1.2 kg with placebo, $p=0.0012$).

## Safety

Statistical analyses of most of the safety data from the studies included in this evidence summary were not reported, which limits the conclusions that can be drawn from them. In GetGoal-X, statistically significantly fewer patients using lixisenatide reported nausea compared with those using exenatide (24.5% compared with 35.1%, $p<0.05$). However, there was no statistically significant difference in the mean total patient assessment of upper gastrointestinal disorders – quality of life score. Statistically significantly fewer patients using lixisenatide reported symptomatic hypoglycaemia compared with those using exenatide (2.5% compared with 7.9%, $p<0.05$).

Gastrointestinal adverse effects are often reported with GLP-1 mimetics. The summary of product characteristics (SPC) states that the most frequently reported adverse reactions during clinical studies, in which more than 2600 people received lixisenatide, were nausea, vomiting and diarrhoea (very common: frequency 1 or more in 10). These reactions were mostly mild and transient. In addition, headache was also very common, as was hypoglycaemia when lixisenatide was used in combination with a sulfonylurea and/or a basal insulin. The SPC notes that GLP-1 mimetics have been associated with a risk of developing acute pancreatitis.

## Evidence strengths and limitations

As with the other GLP-1 mimetics, there are no data from RCTs relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events, or long-term safety data. The evidence of efficacy relates solely to surrogate end points, chiefly reductions in $HbA_{1c}$. The clinical significance of these needs to be judged in the context of the wider evidence base relating to the management of type 2 diabetes, as discussed in the Introduction. In addition, in the studies discussed in this evidence summary the response to placebo on the primary outcome of reductions in $HbA_{1c}$ from baseline was large, which somewhat hampers assessment of lixisenatide's effects.

In all the clinical trials discussed in this evidence summary, allocation was concealed, therefore avoiding an important potential source of bias. In addition, the use of the ANCOVA method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycaemic drugs, baseline $HbA_{1c}$ and country of treatment. Most of the studies were double-blind, but GetGoal-X was open-label, which is a potential source of bias.

As the EMA notes in its guideline on missing data in confirmatory clinical trials, it is unrealistic to expect that all patients in any clinical trial will receive treatment with full compliance to the treatment schedule and with a complete follow-up as per protocol: some patients will drop out of the trial before the scheduled conclusion and among those who stay in, some will have data not recorded for some reason. The guideline states that there is no universally applicable method that adjusts the analysis to take these missing values into account, and different approaches may lead to different conclusions. All the studies discussed in this evidence summary were 24-week studies that used the last observation carried forward (LOCF) approach to take account of missing data. In this approach, regardless of when a patient left the trial (for example, after week 1, week 6 or week 23), the last available result for that patient was carried forward and analysed as though it were the result at the study end.

In the clinical trials discussed in this evidence summary, drop-out rates ranged from 8.6% to 16.1% among patients randomised to lixisenatide, and 5% to 14.9% among those randomised to placebo. The EMA's guideline on missing data in confirmatory clinical trials notes that people who do not complete a clinical trial may be more likely to have extreme values than those who do. Therefore, the loss of these 'non-completers' could lead to an underestimate of variability and therefore artificially narrow the confidence interval for the treatment effect. Because the choice of primary analysis will be based on assumptions that cannot be verified, the EMA guideline advises that it will almost always be necessary to investigate the robustness of trial results through appropriate sensitivity analyses that make different assumptions. Sensitivity analyses were not reported in any of the clinical trials discussed in this evidence summary.

The published analysis of the GetGoal-X non-inferiority study requires additional discussion. The analysis of the modified intention-to-treat (ITT) data set found that lixisenatide was statistically significantly less effective than, but non-inferior to, exenatide for the primary outcome of change in $HbA_{1c}$ from baseline; that is, the upper 95% confidence interval for the difference (0.297 percentage points) did not exceed the pre-specified non-inferiority criterion of 0.4 percentage points. The difference was also less than the criterion of 0.3 percentage points more recently recommended by the EMA in its guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. However, the EMA guidance on the points to consider on switching between superiority and non-inferiority advises that, although in a superiority study the ITT analysis is the analysis of choice, in a non-inferiority study the ITT and per-protocol analyses have equal value and their use should lead to similar conclusions for a robust interpretation of the results. The per-protocol analysis of GetGoal-X was not reported in the published account of GetGoal-X, but the EMA noted in its public assessment report for lixisenatide that that upper 95% confidence interval was 0.315 percentage points in the 'completer' population. This breached the EMA's currently required criterion. The EMA concluded that non-inferiority to exenatide had not been shown robustly and that applying the recommended non-inferiority margin of 0.3 percentage points indicated that the effect of lixisenatide may be inferior to exenatide.

## Context

### Treatment alternatives

The currently licensed glucagon-like peptide-1 (GLP-1) mimetics other than lixisenatide are:

- exenatide

  – Byetta 5 microgram and 10 microgram solutions for injection in prefilled pens (twice-daily use)

  – Bydureon 2 mg powder and solvent for prolonged-release suspension for injection (once-weekly use)

- liraglutide

  – Victoza 6 mg/ml solution for injection in prefilled pen (once-daily use).

The Introduction gives details of NICE recommendations on using both exenatide and liraglutide.

## Costs of treatment alternatives

Pack sizes differ among the GLP-1 mimetics. Yearly costs have therefore been calculated on the basis of costs per 365 days for medication administered each day and costs per 52 weeks for the once-weekly exenatide formulation.

| Drug and usual dosage[a] | Annual cost |
|---|---|
| Exenatide 5 micrograms twice daily | £830.25[b] |
| Exenatide 10 micrograms twice daily | £830.25[b] |
| Exenatide 2 mg once weekly | £953.68[c] |
| Liraglutide 1.2 mg once daily | £954.84[c] |
| Lixisenatide 20 micrograms once daily | £705.75[c] |

[a] The doses shown are taken from the relevant summary of product characteristics, but do not represent the full range that can be used nor do they imply therapeutic equivalence. Liraglutide is also licensed at a dose of 1.8 mg once daily but this is not recommended in NICE technology appraisal guidance 203.

[b] Costs taken from Drug Tariff July 2013.

[c] Costs excluding VAT, taken from MIMS July 2013.

## Estimated impact for the NHS

### Likely place in therapy

NICE has not published guidance specifically related to lixisenatide, but the place of the drug in therapy will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

NICE recommends the use of exenatide or liraglutide in dual or triple therapy in addition to metformin, a sulfonylurea or a glitazone in certain circumstances (see the Introduction for more information). The European Medicines Agency (EMA) noted in its public assessment report for lixisenatide that the effect of lixisenatide on $HbA_{1c}$, when added on to metformin, was clinically relevant. However, the 0.8–0.9 percentage point mean reduction in $HbA_{1c}$ from baseline in the lixisenatide groups in GetGoal-P and GetGoal-M were slightly less than the 1.0 percentage point (11 mmol/mol) reduction specified in NICE guidance as a criterion for continuing treatment with

exenatide or liraglutide in triple or dual therapy beyond 6 months, and the mean difference from placebo was about half of that.

Although the EMA concluded in its public assessment report for lixisenatide that non-inferiority to exenatide had not been shown robustly, it stated that the absolute mean reduction in HbA$_{1c}$ and body weight from baseline produced by lixisenatide in GetGoal-X was of clear clinical relevance, and that lack of proof of non-inferiority could be acceptable considering other benefits, such as once-daily dosing and a lower incidence of nausea and hypoglycaemia.

Weight loss has been seen as a possible pleiotropic effect of glucagon-like peptide-1 (GLP-1) mimetics and is a criterion within NICE guidance for continuing treatment with exenatide or liraglutide in triple therapy in addition to metformin and a sulfonylurea beyond 6 months. There was no statistically significant effect from lixisenatide on body weight compared with placebo in either GetGoal-M or GetGoal-P (lixisenatide plus oral agents). In the 2 trials of lixisenatide in conjunction with basal insulin, body weight reduced to a greater extent with lixisenatide than placebo in GetGoal-L and increased to a lesser extent with lixisenatide than placebo in GetGoal-Duo1. The EMA concluded in its public assessment report for lixisenatide that, overall, the mean difference in body weight with lixisenatide compared with placebo was approximately 1 kg, and that this was of clear clinical relevance and advantageous compared with the increase in weight with some other therapeutic options.

NICE guidance does not currently include the use of any GLP-1 mimetic in combination with insulin. The results of GetGoal-L and GetGoal-Duo1 needs to be considered in that context and also in terms of the likely clinical significance of the observed difference in HbA$_{1c}$ from baseline and in comparison with placebo.

## Estimated usage

The manufacturer estimates that there will be approximately 93,000 people with type 2 diabetes receiving GLP-1 mimetics in the UK by the end of 2013 and that 12,000 (13%) of these people will be using lixisenatide.

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## About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – integrated process statement.

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