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Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

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1 Guidance

- 1.1 Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in '[Type 2 diabetes: the management of type 2 diabetes](#)' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$ [59 mmol/mol] or other higher level agreed with the individual), and the person has:
- a body mass index (BMI) $\geq 35 \text{ kg/m}^2$ in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight **or**
 - a BMI $< 35 \text{ kg/m}^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
- 1.2 Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described in '[Type 2 diabetes: the management of type 2 diabetes](#)' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months).
- 1.3 Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in '[Liraglutide for the treatment of type 2 diabetes mellitus](#)' (NICE technology appraisal 203); that is, only if:
- the person is intolerant of either metformin **or** a sulphonylurea, or a treatment with metformin **or** a sulphonylurea is contraindicated, **and**
 - the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, **or** a treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

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- 1.4 Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described in '[Liraglutide for the treatment of type 2 diabetes mellitus](#)' (NICE technology appraisal guidance 203); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] at 6 months).

2 The technology

2.1 Exenatide prolonged-release suspension for injection (Bydureon, Eli Lilly) has a UK marketing authorisation for the 'treatment of type 2 diabetes mellitus in combination with:

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

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies'. The recommended dose is 2 mg exenatide once weekly by subcutaneous injection. Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Incretin hormones such as GLP-1 enhance glucose-dependent insulin secretion and exhibit other antihyperglycaemic actions. Exenatide improves glycaemic control in patients with type 2 diabetes in several ways, including through enhanced glucose-dependent insulin secretion, and reduced glucose-dependent glucagon secretion.

2.2 The most common adverse drug reactions are mainly gastrointestinal (nausea, vomiting, diarrhoea and constipation), injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache can also occur. Most adverse reactions are mild to moderate in intensity. For full details of side effects and contraindications, see the [summary of product characteristics](#).

2.3 Exenatide prolonged-release suspension for injection costs £73.36 for a pack of four single-dose kits, each containing one vial of exenatide 2 mg powder and a pre-filled syringe of solvent (costs from manufacturer's submission; excludes VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of exenatide prolonged-release suspension for injection and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

Clinical effectiveness

- 3.1 The manufacturer's submission presented evidence on the clinical effectiveness of weekly prolonged-release exenatide (2 mg subcutaneous injection) in patients with type 2 diabetes that was inadequately controlled with oral therapy and/or lifestyle modification based on the DURATION trial programme. Five randomised controlled trials compared weekly prolonged-release exenatide 2 mg with either exenatide 10 micrograms twice daily (DURATION-1 and DURATION-5), sitagliptin 100 mg (DURATION-2), pioglitazone 45 mg (DURATION-2), insulin glargine once daily (DURATION-3) or liraglutide 1.8 mg (DURATION-6).
- 3.2 The primary outcome for all studies was change in HbA_{1c} from baseline to end point (24–30 weeks). Secondary outcomes included changes in body weight, and safety and tolerability. Results were reported for the intention-to-treat populations. Three of the trials had an open-ended extension period (DURATION-1, DURATION-2 and DURATION-3).

3.3 Patients in the trials were broadly similar: aged at least 18 years with a baseline body mass index 25–45 kg/m², HbA_{1c} 7.1–11.0% at screening and stable body weight. Patients enrolled in the DURATION studies were on a mix of different background treatments. Patients in DURATION-1 and DURATION-5 were on a wide range of treatments including diet and exercise alone, metformin alone, metformin and sulphonylurea, thiazolidinedione alone and metformin and thiazolidinedione. Patients in DURATION-3 were either on metformin alone (approximately 70%) or metformin and sulphonylurea (approximately 30%). All patients in DURATION-2 were on metformin alone as background therapy. Information on the background treatments in the DURATION-6 trial which compared prolonged-release exenatide with liraglutide 1.8 mg were submitted as academic in confidence and therefore, have not been presented here. The effectiveness of weekly prolonged-release exenatide 2 mg was compared with exenatide 10 micrograms twice daily in two studies, which demonstrated both reductions in HbA_{1c} and body weight. In both studies, HbA_{1c} reduction was greater with the once-weekly preparation. In DURATION-1 (n = 295), reduction in HbA_{1c} was –1.9% for weekly prolonged-release exenatide versus –1.5% for exenatide twice daily (p = 0.0023). In DURATION-5 (n = 252), reduction in HbA_{1c} was –1.6% for weekly prolonged-release exenatide versus –0.9% for exenatide twice daily (p < 0.0001). Weight loss was similar for the weekly prolonged-release and twice-daily arms in both studies (–3.7 kg for weekly prolonged-release exenatide and –3.6 kg for exenatide twice daily in DURATION-1, p = 0.8916; –2.3 kg for weekly prolonged-release exenatide and –1.4 kg for exenatide twice daily in DURATION-5, p = 0.0514). The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Impact of Weight on Quality of Life Questionnaire, Lite Version (IWQOL-Lite) showed significant improvements from baseline in both treatment arms (p < 0.001 both comparisons) but without any statistically significant differences between the treatment arms.

- 3.4 DURATION-2 (n = 491) compared the effectiveness of weekly prolonged-release exenatide 2 mg plus oral placebo with sitagliptin 100 mg plus injected placebo, and with pioglitazone 45 mg orally plus injected placebo. There was a statistically significant greater reduction in HbA_{1c} with weekly prolonged-release exenatide (-1.55%) compared with sitagliptin (0.92%, p < 0.0001) and pioglitazone (-1.23%, p = 0.0165). Weekly prolonged-release exenatide was associated with a weight loss of 2.3 kg compared with a weight loss of 0.8 kg for sitagliptin (p = 0.0002) and a weight gain of 2.8 kg for pioglitazone (p < 0.0001). Significantly greater improvements in IWQOL-Lite total score were reported for weekly prolonged-release exenatide versus pioglitazone (difference 3.94, 95% confidence interval [CI] 1.28 to 6.61, p = 0.0038). All treatment groups showed statistically significant improvements from baseline on the Psychological and General Well-being Index (PGWB) and DTSQ total scores, with greater improvement in overall treatment satisfaction for weekly prolonged-release exenatide versus sitagliptin (difference 1.61, 95% CI 0.07 to 3.16, p = 0.0406).
- 3.5 Weekly prolonged-release exenatide 2 mg versus insulin glargine once daily was investigated in the DURATION-3 trial (n = 456). There was a statistically significant greater reduction in HbA_{1c} for weekly prolonged-release exenatide compared with insulin glargine (-1.47% versus -1.31%, p = 0.017). Weekly prolonged-release exenatide was associated with a weight loss of 2.6 kg compared with a weight gain of 1.4 kg for insulin glargine (p < 0.001). Patients in both treatment groups reported improvements from baseline to end point in IWQOL-Lite, Binge Eating Scale (BES) and DTSQ total scores. Patients on weekly prolonged-release exenatide showed statistically significant gains in health-related quality of life as measured by EQ-5D. There was no statistically significant difference in quality of life between the weekly prolonged-release exenatide and insulin glargine arms for any of the measures of quality of life.

- 3.6 Weekly prolonged-release exenatide 2 mg was compared with liraglutide 1.8 mg once daily in the DURATION-6 study (n = 911). There was a statistically significant greater reduction in HbA_{1c} with liraglutide 1.8 mg (-1.48%) compared with weekly prolonged-release exenatide (-1.28%, p = 0.002). There was a statistically significant greater weight loss with liraglutide 1.8 mg (-3.6 kg) compared with weekly prolonged-release exenatide (-2.7 kg, p < 0.001). The manufacturer presented confidential evidence on differences in quality of life that cannot be included.
- 3.7 The extension studies (DURATION-1, DURATION-2 and DURATION-3) showed continuation of the benefits of treatment with weekly prolonged-release exenatide. In DURATION-1, patients who completed 52 weeks of treatment with weekly prolonged-release exenatide had similar HbA_{1c} reduction to those who switched from exenatide twice daily to weekly prolonged-release exenatide at week 30. Patients who continued treatment with weekly prolonged-release exenatide reported a statistically significant HbA_{1c} reduction from baseline at 2 years and at 3 years. In DURATION-2, initial 26-week improvements in HbA_{1c} with weekly prolonged-release exenatide were sustained at week 52. HbA_{1c} reduction was also sustained at week 52 in patients who switched from pioglitazone, while switching from sitagliptin increased the reduction in HbA_{1c} at 52 weeks (-1.4%). The difference in weight change between the weekly prolonged-release exenatide and insulin glargine groups was maintained at 84 weeks in the DURATION-3 trial.

- 3.8 The manufacturer presented the effectiveness of weekly prolonged-release exenatide for pre-specified subgroups that were defined by baseline HbA_{1c} (less than 9%, or 9% or greater). Weekly prolonged-release exenatide was associated with a statistically significant reduction in HbA_{1c} compared with exenatide twice daily and sitagliptin (but not pioglitazone) for both subgroups. For the comparison of weekly prolonged-release exenatide with pioglitazone, the reduction in HbA_{1c} reached statistical significance only in patients with HbA_{1c} of 9% or greater. There was a numerically greater HbA_{1c} reduction with weekly prolonged-release exenatide in the subgroups with baseline HbA_{1c} 9% or greater than in the subgroups with HbA_{1c} less than 9% versus exenatide twice daily, sitagliptin and pioglitazone. The manufacturer also presented confidential evidence about HbA_{1c} subgroups from the DURATION-6 trial (weekly prolonged-release exenatide compared with liraglutide 1.8 mg) that cannot be included in this document.
- 3.9 The manufacturer presented the effectiveness of weekly prolonged-release exenatide for subgroups defined by baseline body mass index (less than 30 kg/m², 30 to 35 kg/m² and greater than 35 kg/m²). A post-hoc analysis of HbA_{1c} reduction by body mass index category indicated that there was no relationship between HbA_{1c} reduction and body mass index associated with weekly prolonged-release exenatide treatment.

- 3.10 A network meta-analysis was included to compare the clinical effectiveness of weekly prolonged-release exenatide with liraglutide 1.2 mg (the dose recommended in '[Liraglutide for the treatment of type 2 diabetes](#)' [NICE technology appraisal guidance 203]). A systematic literature review identified 19 randomised controlled trials of weekly prolonged-release exenatide and liraglutide that had common comparators (exenatide twice daily, insulin glargine and placebo). The manufacturer reported the relative effectiveness of each active treatment compared with placebo. All active treatments produced statistically significant reductions in HbA_{1c}. A head-to-head analysis of weekly prolonged-release exenatide versus liraglutide at the different doses was performed. The results of the adjusted analysis for mean difference (95% CI) in HbA_{1c} versus placebo showed that liraglutide 1.8 mg was associated with the biggest reduction in HbA_{1c} (-1.18% [-1.32 to -1.04]) followed by weekly prolonged-release exenatide (-1.15% [-1.31 to -1.00]), liraglutide 1.2 mg (-1.01% [-1.18 to -0.85]), insulin glargine (-0.84% [-1.00 to -0.67]) and exenatide twice daily (-0.82% [-0.94 to -0.70]). Results followed the same trend when controlling for background oral therapy. The manufacturer noted that this demonstrates that the efficacy of weekly prolonged-release exenatide is not statistically significantly different from liraglutide (both 1.2 mg and 1.8 mg doses) in relation to HbA_{1c} reduction. The head-to-head network meta-analysis also reported no significant difference between the comparative efficacy of weekly prolonged-release exenatide and liraglutide (1.2 mg and 1.8 mg doses) for weight change or systolic blood pressure.

Adverse events

- 3.11 The most common adverse effects (occurring in more than 5% of patients) associated with weekly prolonged-release exenatide in the DURATION trials were nausea, diarrhoea and vomiting. The manufacturer noted that the drug was generally well-tolerated; adverse events were generally mild or moderate and were of a similar type and frequency to those observed with exenatide twice daily. Additionally, the rate of adverse events did not vary with background oral antidiabetic therapy (with the exception of a higher incidence of hypoglycaemia with concomitant sulphonylurea use). Weekly prolonged-release exenatide was associated with a lower incidence of gastrointestinal adverse events (35% versus 14–26%) but a higher incidence of injection site-related events compared with exenatide twice daily. Weekly prolonged-release exenatide was associated with low rates of minor hypoglycaemic events (1–3%) in patients who were not taking a concomitant sulphonylurea.

Cost effectiveness

- 3.12 The manufacturer submitted a de novo analysis using the CORE diabetes model to assess the cost effectiveness of weekly prolonged-release exenatide in treating type 2 diabetes that is inadequately controlled on oral antidiabetic therapy, from an NHS and personal social services perspective. In the model, weekly prolonged-release exenatide was used as an alternative to liraglutide 1.2 mg in dual therapy regimens where sulphonylureas, thiazolidinediones and DPP-4 inhibitors are not tolerated or are contraindicated, and as part of triple therapy (as an alternative to exenatide twice daily and liraglutide 1.2 mg).

- 3.13 The CORE model consists of 15 Markov submodels that simulate the major macrovascular and microvascular complications of type 2 diabetes. Patients enter the model at the point where glycaemic control is inadequate on current treatment and they are about to move to the next step in the treatment pathway. The model projects long-term outcomes by taking into consideration baseline patient characteristics (such as ethnicity, gender, age, body mass index, duration of diabetes), past history of complications (for example, previous myocardial infarction or stroke) and physiological parameters (for example, HbA_{1c}, systolic blood pressure and lipids). Each submodel runs simultaneously and in parallel, allowing patients to develop multiple complications within each Markov cycle and over the entire duration of the model.
- 3.14 The manufacturer incorporated data from the DURATION-1, DURATION-2, DURATION-3 and DURATION-5 clinical trials and the network meta-analysis in the economic analyses. Because the trials included a mix of background treatments, the manufacturer assumed that the treatment effects were comparable regardless of their place in treatment (dual and triple therapy) and independent of the stage of disease. Comparators were exenatide twice daily, sitagliptin, pioglitazone, insulin glargine and liraglutide 1.2 mg. Liraglutide 1.8 mg was not included because this dose was not recommended by NICE (NICE technology appraisal guidance 203) so data from the network meta-analysis were used. Six-month data from the DURATION trials were used to populate the model at 1 year and the treatment effect was assumed to be maintained for 5 years until switching to insulin glargine, in line with the modelling in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87) and NICE technology appraisal guidance 203.
- 3.15 Within each submodel, patient characteristics (for example, HbA_{1c} level) were used in risk equations to calculate the probability of experiencing diabetes complications. The risk of experiencing an event was further modified by use and effectiveness of medications, screening (for example, for foot problems or eye complications), and concomitant treatments (for example, aspirin, statins or angiotensin-converting enzyme inhibitors).

- 3.16 After switching to insulin glargine, two different situations were modelled depending on the initial treatment effect. If one treatment caused weight loss and the other caused weight gain (for example, with weekly prolonged-release exenatide compared with pioglitazone and insulin glargine), no change was applied after switching for treatments with initial weight gain but the body mass index reverted to baseline immediately after switching for treatments with initial weight loss. If both treatments caused weight loss (for example, with weekly prolonged-release exenatide compared with sitagliptin, exenatide twice daily and liraglutide), the body mass index for both treatment groups reverted to baseline immediately after switching. The CORE model is not set up to model changes over time, therefore changes in body mass index observed in the DURATION trials were applied to the starting cohort.
- 3.17 Common adverse events were incorporated using incidence rates for nausea and hypoglycaemia from the DURATION trials. The model applied a 6-month disutility for nausea for each comparator and this assumption was tested in the sensitivity analyses. Disutility and associated costs for hypoglycaemic events (included as minor events because there were no events that met the CORE model definition of major hypoglycaemic events) were applied for 5 years until treatment was switched to insulin glargine. The model did not include a disutility associated with injection site reactions in the base case because the DURATION trials showed that injection site reactions were mild and transient and incidence rates were low, although a sensitivity analysis that assessed the impact of this adverse event was also provided.
- 3.18 The risk equations for developing long-term complications were predominantly based on long-term outcome data from the UKPDS and Framingham studies. The model ran in 1-year cycles (after each cycle the profile of each patient was updated for the occurrence of complications and disease progression then used in the next cycle). Exceptions were the foot ulcer/amputation submodel (3-month cycles) and the hypoglycaemia submodel (3-month and 1-day cycles for major and minor events respectively). Each submodel used tracker variables to overcome the memoryless properties of standard Markov models, and allowed interconnectivity and interaction between individual complication submodels.

- 3.19 Base-case assumptions used in the manufacturer's model incorporated a time horizon of 50 years. The first five cycles in the model equated to 5 years of treatment with either weekly prolonged-release exenatide or comparator, then patients in both arms switched to insulin glargine. The base-case model did not incorporate a reduction in HbA_{1c} after switching because treatment effects were applied equally to both arms. For the remaining 45 cycles (from year 6 onwards), the model continued to evaluate utilities and costs from the associated disease complications.
- 3.20 Utility values for the different health states and complications of diabetes were mostly taken from the guidance on liraglutide in type 2 diabetes ([NICE technology appraisal guidance 203](#)) and from [NICE clinical guideline 87](#). A utility value of 0.814 was used as the baseline quality of life value in the model for patients with type 2 diabetes who were free of complications (derived from EQ-5D data in the UKDPS trial). In the model, each health state had a utility value. A total disutility value of -0.04 was used for the subset of patients experiencing nausea and was weighted across the entire population for the first 6 months. For each occurrence of hypoglycaemia, the appropriate disutility relating to minor or major events was applied (-0.012 for major event; -0.004 for a minor event). Injection site reactions were incorporated into the economic analysis via a decrease in utility of -0.011. The decrease in utility was applied for 5 years and weighted across the entire population for each treatment arm according to the proportion of patients who experienced the adverse event from each of the clinical trials. Patients experienced a decrease in their quality of life when they had an event or complication, which was updated after each cycle. For multiple comorbidities, the model selected the utility of the lowest value and used it in subsequent cycles.

- 3.21 The manufacturer used unit costs from the NICE guidance on liraglutide ([NICE technology appraisal guidance 203](#)) where possible for consistency and reference costs were inflated to 2010 levels where appropriate. Total treatment-related costs for type 2 diabetes comprised drug costs and consumable costs (costs associated with self-monitoring of blood glucose and costs of needles for injectable therapies). The frequency of blood glucose monitoring was assumed to be 1 test per day for patients taking insulin and 3 tests per week for patients receiving a sulphonylurea at a cost of £0.33 per test.
- 3.22 Drug acquisition costs for comparators were taken from MIMS (April 2011 edition). Costs of background oral therapies were not included because these were the same across treatment arms in each respective trial. Total annual costs for year 1 to year 5 were £515.00 for pioglitazone 45 mg, £434.65 for sitagliptin 100 mg, £911.99 for exenatide 10 micrograms twice daily (drug costs £829.12), £466.68 for insulin glargine 31.1 IU/day (drug costs £314.12) and £1022.95 for liraglutide 1.2 mg (drug costs £956.96). The total annual cost for weekly prolonged-release exenatide differed across the DURATION studies because blood glucose monitoring requirements were not the same in all trials. Drug costs for weekly prolonged-release exenatide were £956.96 for all studies with additional costs of £17.13 for DURATION-1 and DURATION-5, £15.14 for DURATION-3 and £33.13 for the comparison with liraglutide 1.2 mg. For treatment with insulin glargine (40.0 IU/day) from year 6 onwards, drug costs were £405.43 and total costs were £557.99. No costs were attributed to managing the adverse events included in the model because it is not expected to need NHS resources.
- 3.23 The manufacturer's base-case results showed that weekly prolonged-release exenatide was more costly but was associated with greater life expectancy and more quality-adjusted life years (QALYs) than pioglitazone, sitagliptin and insulin glargine, giving incremental cost-effectiveness ratios (ICERs) of £8624, £6554 and £11,041 per QALY gained respectively. Weekly prolonged-release exenatide dominated exenatide twice daily and liraglutide 1.2 mg because it was associated with greater benefits at a lower cost. Dominance over liraglutide 1.2 mg was the result of a slightly larger predicted reduction in HbA_{1c} with weekly prolonged-release exenatide and reduced needle costs.

- 3.24 A probabilistic sensitivity analysis presented by the manufacturer showed that, at a threshold of £20,000 per QALY, weekly prolonged-release exenatide had a 99–100% probability of being cost effective when compared with pioglitazone, sitagliptin, exenatide twice daily and insulin glargine, and an 87.4% probability of being cost effective compared with liraglutide 1.2 mg.
- 3.25 The manufacturer presented a range of deterministic sensitivity analyses around the confidence limits within the weekly prolonged-release exenatide arm for the main clinical parameters (HbA_{1c}, blood pressure, lipids and body mass index), complication costs and utilities. The ICERs were not sensitive to changes in most of the clinical efficacy, costs and utilities parameters, which generally produced ICERs of under £10,000 per QALY gained for weekly prolonged-release exenatide compared with pioglitazone and sitagliptin, and ICERs of under £14,000 per QALY gained in comparison with insulin glargine. The key drivers of the cost effectiveness of weekly prolonged-release exenatide were the effects on HbA_{1c} and weight, although all of the ICERs for the sensitivity analysis were below £15,000 per QALY gained. Weekly prolonged-release exenatide dominated liraglutide 1.2 mg in all of the analyses with the exception of when HbA_{1c} was set to the lower 95% confidence interval, which led to liraglutide 1.2 mg dominating weekly prolonged-release exenatide. In response to a request by the ERG, the manufacturer conducted a sensitivity analysis that applied the cost of human NPH insulin to the cost-effectiveness estimate of weekly prolonged-release exenatide compared with insulin. This reduced total costs in both arms but increased the net cost from £1709 to £2544 for the prolonged-release exenatide arm over the insulin arm, increasing the ICER of weekly prolonged-release exenatide to £16,493 per QALY gained.

- 3.26 The manufacturer also performed subgroup analyses according to body mass index (30 kg/m² or less, greater than 30 kg/m², at least 30 kg/m² but less than 35 kg/m², and 35 kg/m² or greater) and HbA_{1c} (baseline HbA_{1c} less than 9% or at least 9%). Weekly prolonged-release exenatide was cost effective in each body mass index subgroup compared with pioglitazone, sitagliptin and insulin glargine (with the majority of ICERs being under £10,000 per QALY gained), and continued to dominate exenatide twice daily (that is, weekly prolonged-release exenatide was more effective and less costly). Weekly prolonged-release exenatide was cost effective in both HbA_{1c} subgroups for comparisons with pioglitazone, sitagliptin and insulin glargine, although weekly prolonged-release exenatide was more cost effective in patients with a baseline HbA_{1c} of equal to or greater than 9% (no comparison was made with liraglutide 1.2 mg).
- 3.27 Structural sensitivity analyses, which were conducted by the manufacturer to explore assumptions within the model, yielded results that were all within a relatively narrow range of the base-case estimated cost per QALY and were all below £20,000 per QALY gained. This suggested that the economic modelling is robust to the structural assumptions used.
- 3.28 A scenario analysis was conducted that applied a treatment continuation rule (based on [NICE clinical guideline 87](#)), in which patients only continued treatment if they had a beneficial metabolic response (a reduction of at least 1 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months). Patients who achieved the treatment continuation criteria in either the prolonged-release exenatide or comparator arm continued treatment for 5 years before switching to insulin glargine (base case). The other patients switched to insulin glargine after 1 year. The ICERs improved for weekly prolonged-release exenatide compared with pioglitazone (£2519 per QALY gained versus £8624 per QALY gained in the base case), sitagliptin (£1793 per QALY gained versus £6554 per QALY gained in the base case) and insulin glargine (£5593 per QALY gained versus £11,041 per QALY gained in the base case).

Evidence Review Group comments

- 3.29 The ERG noted all of the relevant studies had been included in the manufacturer's submission and that they were all of good quality.
- 3.30 The ERG commented on the suitability of the DURATION trials for addressing the decision problem. They noted that the populations in the DURATION-1 and DURATION-5 trials do not fully reflect the use of GLP-1 analogues in clinical practice (triple therapy). Patients in these trials were taking a range of background treatments, with 43–46% receiving monotherapy and 36–39% dual therapy. The ERG also did not consider the DURATION-2 trial, which compared weekly prolonged-release exenatide with pioglitazone and sitagliptin, to be relevant to UK clinical practice because patients in the trial were taking metformin monotherapy and were randomised to receive dual therapy with metformin plus either weekly prolonged-release exenatide, sitagliptin or pioglitazone. It noted that this is at variance with [NICE clinical guideline 87](#), which recommends adding a sulphonylurea (or oral alternative such as pioglitazone) to metformin. The ERG also advised that in routine care a (relatively) inexpensive oral drug would be offered before an expensive injectable drug. The ERG, however, considered the DURATION-6 trial (which used a 1.8 mg daily dose of liraglutide as the comparator) better reflects clinical practice because 64% of the patients were receiving dual therapy.
- 3.31 The ERG considered the network meta-analysis that compared weekly prolonged-release exenatide with liraglutide 1.2 mg to be consistent with the scope for this appraisal, noting that it was good quality and showed similar efficacy between the two drugs, although there was a small disutility associated with additional injections with liraglutide. The ERG noted that the size of the difference in Hb_{A1c} between the liraglutide doses (1.2 mg and 1.8 mg) could hypothetically affect the cost-effectiveness calculations. The ERG's meta-analysis (which excluded a monotherapy trial that was included in the manufacturer's analysis) estimated that the difference in Hb_{A1c} was 0.10% compared with the manufacturer's estimate of 0.17%.

- 3.32 The ERG considered that there may be some structural uncertainty around the CORE model because it appeared to model the evolution of HbA_{1c}, systolic blood pressure and the ratio of total cholesterol to HDL cholesterol quite differently to the UKPDS outcomes model. In particular, CORE appeared to maintain a proportion of the initial net effects between the treatment arms indefinitely, whereas the UKPDS outcomes model appeared to model these net effects as tending to zero over time. The ERG also considered that there was uncertainty in the assumption that treatment duration will be 5 years because of the absence of long-term clinical data.
- 3.33 The ERG considered the direct health-related quality of life impact from changes in body mass index to be a model driver because its exclusion increased the ICER for weekly prolonged-release exenatide when compared with pioglitazone (£17,772 per QALY gained compared with £8624 per QALY gained in the base case) and insulin glargine (£16,605 per QALY gained compared with £11,041 per QALY gained in the base case). The ERG observed that assumed duration of therapy is also a model driver, with cost effectiveness improving with a shorter duration of therapy before switching. The ERG noted that all the modelling found that weekly prolonged-release exenatide produced similar patient benefits and costs as liraglutide 1.2 mg, although the sensitivity analyses demonstrated that the small net effects cause the analysis to swing from the base case of weekly prolonged-release exenatide dominating liraglutide 1.2 mg to it sometimes being dominated by liraglutide 1.2 mg.

Evidence Review Group exploratory analyses

- 3.34 The ERG noted that the model applied lifetime weight changes, which may bias against treatments that increase weight. The ERG undertook sensitivity and scenario analyses on the manufacturer's model to investigate the impact of lifetime maintenance of weight gain on health-related quality of life and the impact of individual clinical effects. A sensitivity analysis in which the disutility associated with increasing weight was only applied for 5 years (that is, before switching treatment to insulin glargine) increased the ICER of weekly prolonged-release exenatide from £8624 per QALY gained to £12,052 per QALY gained for the comparison with pioglitazone and from £11,041 per QALY gained to £12,839 per QALY gained for the comparison of weekly prolonged-release exenatide with insulin glargine.
- 3.35 The ERG investigated how the individual clinical effects (changes in body mass index [with and without applying any direct disutility from weight changes], HbA_{1c}, systolic blood pressure, and cholesterol and triglycerides) observed within the DURATION trials contributed to anticipated patient outcomes and costs. For the comparisons of weekly prolonged-release exenatide with exenatide twice daily, the ERG considered the main benefit to be derived from changes in HbA_{1c}, with lipid changes also contributing. Changes in HbA_{1c} had the greatest effect on cost. For the comparison with pioglitazone, the patient benefits were shared almost equally between the direct impact of weight changes and changes in HbA_{1c}. Costs were predominantly reduced because lower HbA_{1c} levels will reduce complication rates. For the comparison with insulin glargine, the largest patient benefit was from the direct impact of weight changes, but only the change in HbA_{1c} significantly affected costs. For the comparison with liraglutide 1.2 mg, only HbA_{1c} has any significant impact on both benefits and costs.
- 3.36 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of weekly prolonged-release exenatide, having considered evidence on the nature of type 2 diabetes and the value placed on the benefits of weekly prolonged-release exenatide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the clinical treatment pathway for type 2 diabetes. The aim of treatment is to achieve good control of blood glucose levels (which is reflected in HbA_{1c} levels) whilst minimising complications such as weight gain and hypoglycaemia. The Committee heard from clinical specialists that the choice of treatment is individualised for each patient, and that current UK practice broadly follows NICE guidance ([NICE clinical guideline 87](#)) which recommends a stepwise approach that includes using diet and exercise, various antidiabetic drugs and insulin. The Committee heard from clinical specialists that the understanding of the precise mode of action of GLP-1 agonists is still evolving. If GLP-1 agonists simply stimulated islet cells, they would not be expected to have significant therapeutic benefit at a late stage of the disease, which nevertheless appears to be the case. The Committee also heard from clinical specialists that there is a trend towards reduced use of sulphonylurea (because of the associated weight gain and the high incidence of hypoglycaemia compared with other oral treatments) and pioglitazone (because of long-term safety concerns over bladder cancer). The Committee was aware that clinical opinion was moving away from sulphonylurea use but also noted that it had been decided that NICE clinical guideline 87 should be updated (expected publication date to be confirmed) and anticipated that changing trends in diabetes management would be addressed in the updated guidance when the whole evidence base had been reviewed. There would also be an opportunity to review the weight and other criteria for initiating GLP-1 agonists in the guidance.

- 4.3 The Committee heard evidence from the patient expert that people with type 2 diabetes may be reluctant to start treatment with insulin or wish to avoid insulin therapy because of fear of hypoglycaemia and its impact on their lifestyle (for example, the threat of losing their driving licence). The patient expert stated the main benefits of weekly prolonged-release exenatide to be improved quality of life associated with a once-weekly treatment regimen, which would reduce the lifestyle impact of managing type 2 diabetes, as well as improved glycaemic control and weight loss, which are also seen with other GLP-1 agonists. The Committee heard from the patient expert that a once-weekly regimen would be advantageous for patients who rely on a carer to administer treatment because they are unable to self-administer injections. The Committee recognised the demands that managing type 2 diabetes places on patients and concluded that an effective once-weekly regimen would be associated with important potential benefits for patients but that on current evidence GLP-1 agonists would not replace insulin (although they may offer an opportunity to delay insulin therapy in some patients).
- 4.4 The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of weekly prolonged-release exenatide, noting that the evidence came from five clinical trials and a network meta-analysis. The Committee considered the comparators included in the trials for triple therapy to be generally appropriate but noted that insulin glargine was the comparator in the DURATION-3 trial instead of human NPH insulin, which is recommended for routine use in [NICE clinical guideline 87](#). The Committee considered the comparators used in the trials with dual therapy to be broadly appropriate but noted the significant absence of a trial comparing weekly prolonged-release exenatide with a sulphonylurea. The Committee concluded that the comparators in the DURATION trials were broadly, but not specifically, relevant to clinical practice in the UK.

- 4.5 The Committee considered the patient populations included in the clinical trials. The Committee noted that patients were taking a mix of different background treatments comprising lifestyle modification and different drug regimens in three of the trials (DURATION-1, DURATION-5 and DURATION-6). It particularly noted that the trials which compared weekly prolonged-release exenatide with exenatide twice daily (DURATION-1 and DURATION-5) included patients who were treated by diet and exercise alone. It also noted that the range of background treatments produced up to eight subgroups with different background treatments in each of these two trials. In addition, in the trial that compared weekly prolonged release exenatide with insulin glargine (DURATION-3), 70% of patients were taking metformin alone as background treatment whereas NICE clinical guideline 87 recommends adding a second oral agent to metformin before adding insulin. DURATION-2 compared the addition of weekly prolonged-release exenatide with sitagliptin or pioglitazone, all in combination with metformin monotherapy. This combination is not recommended in current guidance unless a sulphonylurea is contraindicated or not tolerated, or there is a significant risk of hypoglycaemia ([NICE clinical guideline 87](#)). In addition, DURATION-2 did not include any European centres. The Committee therefore had reservations about how well the trial populations reflected current UK clinical practice. The Committee considered that the nature of the evidence (including the wide mix of background treatments in some trials) does not allow inferences to be drawn on a specific place for weekly prolonged-release exenatide in the treatment pathway as dual- and triple-therapy agents. It concluded that the DURATION trials were sufficiently relevant to the decision problem to allow use of the data in evaluating clinical effectiveness, but that caution should be used when generalising data where the trials differed from normal UK clinical practice.
- 4.6 The Committee considered the evidence comparing weekly prolonged-release exenatide with exenatide twice daily (DURATION-1 and DURATION-5). It considered weekly prolonged-release exenatide to be more effective in lowering HbA_{1c} than exenatide twice daily and to have similar efficacy in inducing weight loss and improving quality of life. The Committee concluded that weekly prolonged-release exenatide is more clinically effective in reducing HbA_{1c} than the twice-daily preparation and that this appeared consistent across differing background treatments.

- 4.7 The Committee considered the evidence comparing weekly prolonged-release exenatide with sitagliptin and pioglitazone (DURATION-2). The Committee concluded that the trial demonstrated that, in combination with metformin, weekly prolonged-release exenatide was more clinically effective than both sitagliptin and pioglitazone for the outcomes of HbA_{1c} reduction and weight loss.
- 4.8 The Committee considered the evidence comparing weekly prolonged-release exenatide with insulin (DURATION-3). The Committee noted the absence of any clinical data comparing weekly prolonged-release exenatide with human NPH insulin, which is the recommended insulin in [NICE clinical guideline 87](#), and that 70% of patients in the DURATION-3 study were taking metformin monotherapy as background treatment (see [section 3.3](#)). The Committee considered weekly prolonged-release exenatide to have greater efficacy than insulin glargine for reducing HbA_{1c}. The Committee also noted that treatment with weekly prolonged-release exenatide resulted in weight loss and treatment with insulin glargine produced weight gain. The Committee concluded that weekly prolonged-release exenatide is more clinically effective than insulin glargine in reducing HbA_{1c}, although there is uncertainty about how this can be applied to UK clinical practice because of the small number of patients in DURATION-3 trial (30%) who were on standard dual therapy

- 4.9 The Committee considered evidence from the randomised controlled trial of weekly prolonged-release exenatide with liraglutide 1.8 mg (DURATION-6) and the network meta-analysis which compared weekly prolonged-release exenatide with liraglutide 1.2 mg. The Committee noted that there was significantly greater HbA_{1c} reduction and weight loss with liraglutide 1.8 mg than with weekly prolonged-release exenatide. However, the Committee noted that this dose of liraglutide is not recommended by NICE and accepted the validity of the network meta-analysis that showed there was no statistically significant difference between the clinical effects of weekly prolonged-release exenatide and liraglutide 1.2 mg (the dose that was recommended in [NICE technology appraisal guidance 203](#)). The Committee heard from clinical specialists that there were no clinically important differences between the GLP-1 agonists. The Committee therefore concluded that weekly prolonged-release exenatide and liraglutide 1.2 mg had similar efficacy in the treatment of type 2 diabetes.

- 4.10 The Committee discussed the likely duration of effectiveness of weekly prolonged-release exenatide. The Committee noted that the clinical trials provided evidence that the effect of weekly prolonged-release exenatide on outcomes on reduction in HbA_{1c} and weight loss persisted for up to 3 years but that no longer-term data are available. Clinical specialists advised that because GLP-1 agonists initiate a dual physiological response by increasing insulin secretion and suppressing glucagon secretion, it is difficult to predict the length of time they will be effective because they could still have an antihyperglycaemic effect after beta cells have stopped producing insulin. They further noted that consequently there may be differences in the degree and duration of effect of weekly prolonged-release exenatide depending on how long a patient has had type 2 diabetes. The Committee also heard from the clinical specialists that younger people are increasingly presenting with type 2 diabetes and, although it is not currently known how long weekly prolonged-release exenatide will be efficacious, glycaemic control could potentially be maintained for 5 years and possibly up to 15–20 years. If ultimately proven to have a prolonged therapeutic effect, GLP-1 agonists might even allow some people who currently need insulin to manage their diabetes without insulin (co-administration with insulin is not presently covered by the UK marketing authorisations for any of the GLP-1 agonists). The Committee concluded that there is presently insufficient evidence to determine the duration of the therapeutic effect of weekly prolonged-release exenatide.
- 4.11 The Committee discussed the relevance of the surrogate endpoints (notably HbA_{1c}) used in the clinical trials as predictors of clinical outcomes. The Committee heard from the clinical specialists that UKPDS data showed that a 1% reduction in HbA_{1c} was associated with a 37% reduction in microvascular complications and a 16% reduction in myocardial infarction. The Committee concluded that HbA_{1c} was an appropriate surrogate marker in type 2 diabetes but noted that there was a need for long-term efficacy and safety data with weekly prolonged-release exenatide, particularly relating to cardiovascular outcomes.

- 4.12 The Committee discussed the treatment continuation criteria for GLP-1 agonists ([NICE clinical guideline 87](#) and [NICE technology appraisal 203](#)), which specify both a reduction of 1 percentage point HbA_{1c} **and** weight loss of at least 3% of initial body weight at 6 months. The Committee noted that the Association of British Clinical Diabetologists' audit shows that there is a complex relationship between HbA_{1c} and weight loss and that it is not clear how much of a fall in HbA_{1c} can be attributed to reduced body weight. The Committee noted that the evidence for these criteria could be reviewed when the clinical guideline for type 2 diabetes (NICE clinical guideline 87) is updated. The Committee therefore concluded that the continuation rules in current NICE guidance are also appropriate for recommendations on treatment with weekly prolonged-release exenatide.
- 4.13 The Committee considered the adverse events associated with weekly prolonged-release exenatide. The Committee noted that the adverse events were generally mild to moderate in intensity and that nausea, which was the most common adverse event, decreased over time. The Committee also noted that the incidence of hypoglycaemia was low. The Committee concluded that the adverse-events profile of weekly prolonged-release exenatide was acceptable.
- 4.14 The Committee considered the cost effectiveness of weekly prolonged-release exenatide compared with exenatide twice daily, liraglutide 1.2 mg, pioglitazone, sitagliptin and insulin glargine in the manufacturer's submission and the critique and exploratory analyses provided by the ERG. The Committee noted this model was also used in NICE technology appraisal guidance 203 and was acceptable, although it noted that these diabetes models are generally rather outdated because they are based on data that are 20 years old (UKPDS). In the absence of more recent data, the Committee concluded, with some reservations, that the CORE model which formed the basis of the manufacturer's submission was acceptable for assessing the cost effectiveness of weekly prolonged-release exenatide.

- 4.15 The Committee discussed the assumption in the manufacturer's model that treatment with weekly prolonged-release exenatide will last for 5 years before a switch to insulin is needed. The Committee noted that there was no clinical evidence to support this and that the duration was chosen by the manufacturer for consistency with previous technology appraisals. The Committee considered the sensitivity analyses on the duration of treatment before patients switched to insulin. It noted that reducing the treatment duration from 5 years (in the base case) to 3 years reduced the ICER, and increasing the treatment duration to 8 years increased the ICER of weekly prolonged-release exenatide compared with each of the comparators. Based on evidence from the clinical specialists, the Committee concluded that it is plausible that people may be on weekly prolonged-release exenatide for 5 years although it still had concerns over the validity of that assumption, and considered that it could be a significant underestimate.
- 4.16 The Committee considered the key drivers of cost effectiveness based on the manufacturer's deterministic sensitivity analyses. It noted that the effects of weekly prolonged-release exenatide on HbA_{1c} and weight were key drivers, and that reducing the efficacy of weekly prolonged-release exenatide to the lower 95% confidence interval for HbA_{1c} or weight increased the ICERs of weekly prolonged-release exenatide compared with most comparators. The Committee was aware that when the lower 95% confidence interval for HbA_{1c} was used in the sensitivity analysis, the comparison of weekly prolonged-release exenatide with liraglutide 1.2 mg changed from weekly prolonged-release exenatide being dominant in the base case to liraglutide dominating in the sensitivity analysis. The Committee considered this was because of the similar efficacy of weekly prolonged-release exenatide and liraglutide. The Committee concluded that the calculated base-case ICERs for weekly prolonged-release exenatide compared with exenatide twice daily, sitagliptin, pioglitazone and insulin glargine could be considered robust to sensitivity analyses, but the ICER compared with liraglutide 1.2 mg was not stable because the two drugs have similar efficacy and have only modest differences in cost.

- 4.17 The Committee considered the manufacturer's base-case model and noted that the ICERs for weekly prolonged-release exenatide versus exenatide twice daily, liraglutide 1.2 mg, pioglitazone, sitagliptin and insulin glargine, plus additional analyses using costs for human NPH insulin were below £20,000 per QALY gained and that the probabilistic sensitivity analysis also showed that weekly prolonged-release exenatide had a high probability of cost effectiveness at £20,000 per QALY gained. The Committee also noted that these ICERs did not reflect the potential differential cost effectiveness of weekly prolonged-release exenatide when used at different parts of the treatment pathway. The Committee therefore considered that the use of weekly prolonged-release exenatide should be considered separately as part of dual and triple therapy compared with alternative treatments at these steps in the pathway in line with the current recommendations for GLP-1 agonists ([NICE clinical guideline 87](#) and [NICE technology appraisal guidance 203](#)), which best reflect clinical practice in the UK.
- 4.18 The Committee examined the subgroup analyses according to baseline HbA_{1c} and baseline body mass index. The Committee noted that weekly prolonged-release exenatide was cost effective regardless of baseline HbA_{1c} subgroup but that there seemed to be improved cost effectiveness in the group with baseline HbA_{1c} of 9% or greater. The Committee heard from clinical specialists that in clinical practice the glycaemic response to GLP-1 agonists is more pronounced in people with a higher baseline HbA_{1c}. The Committee noted that the results according to body mass index were mixed but that the ICER decreased for all comparisons versus the base case in the subgroup where body mass index was 35 kg/m² or greater. The Committee concluded that the results of the subgroup analysis were consistent with the NICE guidance for the use of GLP-1 agonists ([NICE clinical guideline 87](#) and [NICE technology appraisal guidance 203](#)) in people with a higher body mass index plus associated obesity-related problems and people with poorly controlled blood glucose.

- 4.19 The Committee considered a scenario analysis in which the treatment continuation criteria for GLP-1 agonists were applied (NICE clinical guideline 87 and NICE technology appraisal guidance 203) instead of the 5-year treatment duration that was applied to all patients in the base case. The Committee noted that applying the treatment continuation criteria reduced the ICER of weekly prolonged-release exenatide for all comparisons (sitagliptin, pioglitazone and insulin glargine). The Committee concluded that the treatment continuation criteria and definition of metabolic response for GLP-1 agonists that have been previously applied in NICE guidance would also be relevant to weekly prolonged-release exenatide.
- 4.20 The Committee considered the potential use of weekly prolonged-release exenatide compared with exenatide twice daily and liraglutide as part of triple therapy in people with a high body mass index (equal to or greater than 35 kg/m²) who have inadequate glycaemic control (HbA1c equal to or greater than 7.5%) and other obesity-related problems. The Committee considered weekly prolonged-release exenatide to be more clinically effective than exenatide twice daily and have similar efficacy to liraglutide 1.2 mg in terms of glycaemic control. The Committee further noted that weekly prolonged-release exenatide dominated exenatide twice daily and liraglutide in the base case and continued to dominate exenatide twice daily in all sensitivity analyses. The Committee noted that the slightly lower administration costs associated with weekly prolonged-release exenatide compared with liraglutide were related to the cost of needles. The Committee concluded that although weekly prolonged-release exenatide appeared marginally more cost effective than liraglutide 1.2 mg, weekly prolonged-release exenatide did not offer sufficient evidence of additional benefits to justify differential recommendation of GLP-1 agonists in triple therapy. The Committee therefore concluded that weekly prolonged-release exenatide is a cost-effective alternative to exenatide twice daily and liraglutide 1.2 mg in triple therapy as currently recommended in NICE guidance.

4.21 The Committee considered the potential use of weekly prolonged-release exenatide compared with insulin in triple therapy regimens. It noted that GLP-1 agonists (exenatide and liraglutide) are used to delay insulin therapy in selected patients as recommended in NICE guidance ([NICE clinical guideline 87](#) and [NICE technology appraisal guidance 203](#)). The Committee was satisfied that, despite the use of insulin glargine instead of the less expensive human NPH insulin in the DURATION-3 trial and the major uncertainty related to the duration of therapy, weekly prolonged-release exenatide is likely to be as cost effective as the other GLP-1 agonists compared with starting insulin for these selected patients. During consultation the Committee received a comment from a consultee that the recommendation for the use of prolonged-release exenatide in triple therapy in patients with a body mass index of less than 35kg/m² and obesity-related problems; and where therapy with insulin would have significant occupational implications was too restrictive. The consultee suggested that prolonged-release exenatide should also be considered in patients for whom insulin therapy would have a negative impact on quality of life. The Committee considered that because clinical practice was broadly in line with NICE clinical guideline 87, there would need to be a good evidence-based justification for increasing the use of GLP-1 agonists (including prolonged-release exenatide) in triple therapy beyond that of current NICE guidance. The Committee concluded that weekly prolonged-release exenatide should be recommended for use in triple therapy in the same way as the existing GLP-1 agonists (NICE clinical guideline 87 and NICE technology appraisal guidance 203).

4.22 The Committee considered the potential use of weekly prolonged-release exenatide as part of dual therapy. It noted that no trial had been carried out by the manufacturer to compare metformin plus weekly prolonged-release exenatide with metformin plus sulphonylurea, which is the recommended first-line dual therapy option in NICE clinical guideline 87. The Committee heard from the clinical specialists that they were concerned about the incidence of hypoglycaemia associated with sulphonylureas, which they considered to be underestimated, and that dual therapy alternatives to sulphonylureas would be welcomed. The Committee discussed a trial of liraglutide that had been discussed in a previous appraisal, which found no statistically significant difference between the GLP-1 agonist and a sulphonylurea in reducing HbA1c when given in combination with metformin (NICE technology appraisal guidance 203). The Committee concluded that there was no evidence that weekly prolonged-release exenatide was as effective or more effective than sulphonylureas, and that weekly prolonged-release exenatide plus metformin could not be recommended as a substitute for metformin in combination with sulphonylurea in dual therapy.

4.23 The Committee discussed the use of weekly prolonged-release exenatide in people who are unable to take sulphonylureas as a second-line agent in combination with metformin. The Committee did not consider that metformin in combination with a GLP-1 agonist was current routine NHS practice and noted that adding a GLP-1 agonist to metformin in preference to oral alternatives to sulphonylureas (pioglitazone and DPP-4 inhibitors) had the potential to alter the established and recommended treatment pathway for managing diabetes, particularly if sulphonylureas became less commonly prescribed. Therefore, considerable certainty about the clinical effectiveness, duration of effect and cost effectiveness would be needed before introducing a new treatment at this stage in the pathway. The Committee considered that there was high uncertainty associated with the potential use of weekly prolonged-release exenatide compared with greater volumes of evidence and clinical experience for pioglitazone and DPP-4 inhibitors. The Committee further noted that the DURATION-2 study, which compared weekly prolonged-release exenatide with pioglitazone and sitagliptin, had a relatively small population with approximately 165 patients in each treatment arm, and did not have any European centres. The cost of pioglitazone may also reduce in the near future because its UK patent protection has recently expired. The Committee also considered the uncertainty related to the duration of action of this combined treatment, which could have a major impact on the cost effectiveness. It concluded that there was at present insufficient evidence to recommend weekly prolonged-release exenatide in dual therapy for all patients who cannot tolerate sulphonylureas.

4.24 The Committee considered the potential place of weekly prolonged-release exenatide as part of dual therapy compared with liraglutide 1.2 mg in people who are not able to take either metformin or a sulphonylurea and are also unable to take pioglitazone or DPP-4 inhibitors (the limited population for whom liraglutide 1.2 mg is currently recommended as dual therapy). The Committee considered the similar clinical and cost effectiveness of weekly prolonged-release exenatide and liraglutide 1.2 mg, and noted that the alternatives for these patients were limited to monotherapy with an oral antidiabetic agent or early initiation of insulin therapy. The Committee noted that any differences in cost effectiveness between GLP-1 agonists were likely to be too small to justify making differential recommendations for the use of GLP-1 agonists in dual therapy. The Committee therefore concluded that weekly prolonged-release exenatide could be an option for dual therapy in patients who cannot take either metformin or sulphonylureas and are also unable to take thiazolidinediones and DPP-4 inhibitors. The Committee considered whether weekly prolonged-release exenatide was innovative and provided a major change in the management of type 2 diabetes. The Committee considered the main benefit of weekly prolonged-release exenatide to be that patients need fewer injections (weekly versus daily), which reduces the impact of managing type 2 diabetes on the daily lives of patients and carers. It has been suggested that this benefit may improve adherence although there is currently no evidence to support this hypothesis. The Committee concluded that weekly prolonged-release exenatide does not represent a major change in the management of type 2 diabetes but is a sustained-release preparation of a currently available treatment.

4.25 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. The Committee heard from the patient expert that a particular benefit from this treatment could be derived for people who need assistance with injections because of the reduced frequency of injections compared with other therapies. During consultation the Committee was also made aware that the uptake of insulin is reportedly low in people of South Asian family origin and there is evidence that compliance with oral medication is also poor. It was suggested that weekly prolonged-release exenatide would be a good alternative for these patients. Poor medical attendance and adherence to treatment was acknowledged by the clinical specialist, and although the causes were unclear, it was considered that this might be associated with cultural preference and concerns about conventional therapy. Nevertheless, the Committee concluded there was at present no evidence that a weekly injected preparation would improve treatment adherence or outcomes in any patient group to justify differential recommendations for weekly prolonged-release exenatide.

Summary of Appraisal Committee's key conclusions

TA248 (STA)	Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes	Section
Key conclusions		

<p>In triple therapy regimens, exenatide prolonged-release suspension for injection (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87). In dual therapy regimens, exenatide prolonged-release suspension for injection (in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in 'Liraglutide for the treatment of type 2 diabetes mellitus' (NICE technology appraisal 203).</p> <p>The Committee considered weekly prolonged-release exenatide to be more effective than exenatide twice daily and is similar in efficacy to liraglutide 1.2 mg. The Committee further considered weekly prolonged-release exenatide to be cost effective compared to exenatide twice daily and liraglutide 1.2 mg and did not see any reason to depart from the recommendations of current clinical guidance.</p>		<p>1.1, 1.3 4.21, 4.22, 4.25</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the clinical specialists that hypoglycaemia associated with sulphonylurea use is considered to be underestimated and there is a trend to reduced sulphonylurea use and to reduced pioglitazone use (because of long-term safety concerns over bladder cancer).</p>	<p>4.2, 4.23</p>
	<p>The patient expert stated that people with type 2 diabetes may be reluctant to start treatment with insulin or wish to avoid insulin therapy because of fear of hypoglycaemia and its impact on their lifestyle.</p>	<p>4.3</p>
<p>The technology</p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The main benefit of weekly prolonged-release exenatide to patients is the need for fewer injections (weekly versus daily). However, the Committee concluded that weekly prolonged-release exenatide does not represent a major change in the management of type 2 diabetes and no case was made that linked health-related benefits to specific innovative characteristics of weekly prolonged-release exenatide.</p>	<p>4.25</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee concluded that weekly prolonged-release exenatide should be recommended for use in triple and dual therapy in the same way as the existing GLP-1 agonists in NICE clinical guideline 87 and NICE technology appraisal guidance 203.</p>	<p>4.21, 4.22, 4.25</p>
<p>Adverse effects</p>	<p>The most common adverse drug reactions are mainly gastrointestinal (nausea, vomiting, diarrhoea and constipation), injection site reactions, hypoglycaemia (with a sulphonylurea) and headache. Most adverse reactions are mild to moderate in intensity. The Committee concluded that the adverse-events profile of weekly prolonged-release exenatide was acceptable.</p>	<p>2.2, 3.17, 4.13</p>
<p>Evidence for clinical effectiveness</p>		

<p>Availability, nature and quality of evidence</p>	<p>The Committee noted that the evidence in the manufacturer's submission came from five clinical trials and a network meta-analysis. The randomised controlled trials compared weekly prolonged-release exenatide with either exenatide 10 micrograms twice daily, sitagliptin 100 mg, pioglitazone 45 mg, insulin glargine once daily or liraglutide 1.8 mg. A network meta-analysis was included to compare the clinical effectiveness of weekly prolonged-release exenatide with liraglutide 1.2 mg (the dose recommended in NICE technology appraisal guidance 203). The Committee noted the significant absence of a trial comparing weekly prolonged-release exenatide with a sulphonylurea.</p>	<p>3.1, 3.12, 4.4, 4.5</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee considered the comparators included in the trials for dual therapy and triple therapy to be generally appropriate but noted that insulin glargine was the comparator in the DURATION-3 trial instead of human NPH insulin, which is recommended for routine use in NICE clinical guideline 87.</p>	<p>4.4</p>
	<p>The Committee noted that patients in the clinical trials were taking a mix of different background treatments comprising lifestyle modification and different drug regimens in three of the trials. It considered that the nature of the evidence (including the wide mix of background treatments in some trials) does not allow conclusions to be drawn on a specific place for weekly prolonged-release exenatide in the treatment pathway. Although the Committee had reservations about how well the trial populations reflected current UK clinical practice, it concluded that they were sufficiently relevant to the decision problem to allow use of the data.</p>	<p>4.5</p>

<p>Uncertainties generated by the evidence</p>	<p>There was uncertainty about the duration of the therapeutic effect of weekly prolonged-release exenatide because current evidence show clinical outcomes persisting for up to 3 years and no longer-term data are available. While HbA_{1c} was considered an appropriate surrogate marker in type 2 diabetes by the Committee, it was noted that long-term efficacy and safety data with weekly prolonged-release exenatide, particularly relating to cardiovascular outcomes, are needed.</p>	<p>4.10, 4.11</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The UK marketing authorisation for exenatide prolonged-release suspension for injection is for the 'treatment of type 2 diabetes mellitus in combination with:</p> <ul style="list-style-type: none"> • metformin • sulphonylurea • thiazolidinedione • metformin and sulphonylurea • metformin and thiazolidinedione <p>in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies'.</p>	<p>2.1</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>There was evidence from the DURATION trials that treatment with weekly prolonged-release exenatide is more clinically effective than exenatide twice daily in reducing HbA_{1c} (and that this appeared consistent across differing background treatments) and has similar efficacy to liraglutide 1.2 mg. The Committee concluded that, in combination with metformin, weekly prolonged-release exenatide was more clinically effective than pioglitazone and sitagliptin. The Committee also concluded that weekly prolonged-release exenatide is more clinically effective than insulin glargine although this conclusion is associated with uncertainty because of the small number of patients in DURATION-3.</p>	<p>4.6,4.7, 4.8, 4.9</p>
<p>Evidence for cost effectiveness</p>		

<p>Availability and nature of evidence</p>	<p>The Committee considered the cost effectiveness of weekly prolonged-release exenatide compared with exenatide twice daily, liraglutide 1.2 mg, pioglitazone, sitagliptin and insulin glargine and the critique and additional analyses provided by the ERG. The Committee noted that this model was also used in NICE technology appraisal guidance 203 and was acceptable, although it noted that these diabetes models are generally rather outdated because they are based on data that are 20 years old (UKPDS). In the absence of more recent data, the Committee concluded, with some reservations, that the CORE model which formed the basis of the manufacturer's submission was acceptable for assessing the cost effectiveness of weekly prolonged-release exenatide.</p>	<p>4.14, 4.15</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The assumption that in the base case of the manufacturer's model that treatment with weekly prolonged-release exenatide will last for 5 years before a switch to insulin glargine is not supported by any clinical evidence. The assumption was chosen by the manufacturer for consistency with previous technology appraisals; changes in duration of effect impacted the ICER.</p>	<p>4.16</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee was aware that the model was also used in NICE technology appraisal guidance 203 and included utility values for quality of life and nausea associated with treatment. As a sensitivity analysis, the model included a disutility value associated with injection site reactions.</p>	<p>3.20, 4.14</p>
	<p>The Committee considered the main benefit of weekly prolonged-release exenatide to be that patients need fewer injections (weekly versus daily), which reduces the impact of managing type 2 diabetes on the daily lives of patients and carers.</p>	<p>4.24</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No specific groups were identified in which weekly prolonged-release exenatide was particularly cost effective.</p>	<p>4.18</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The effects of weekly prolonged-release exenatide were driven by changes in HbA_{1c} and weight.</p>	<p>4.16</p>

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted the ICERs presented in the manufacturer's submission were not specific to the place of weekly prolonged-release exenatide in triple and dual therapy regimens. The Committee did however, consider on the basis of the ICERs presented in the manufacturer's submission, that weekly prolonged-release exenatide is likely to be cost effective when used in the same place in the treatment pathway as twice daily exenatide and liraglutide 1.2 mg were currently recommended.	4.17
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	
End-of-life considerations	Not applicable to this appraisal.	
Equalities considerations and social value judgements	The Committee concluded there was at present no evidence that a weekly injected preparation would improve treatment adherence or outcomes in any patient group to justify differential recommendations for the use of weekly exenatide.	4.25
	The restrictions outlined in the recommendations (and also in NICE clinical guideline 87 and NICE technology appraisal guidance 203) incorporate appropriate adjustment of BMI by ethnic group.	1.1

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 NICE has developed tools to help organisations put this guidance into practice (listed below).
- A costing statement explaining the resource impact of this guidance.
 - Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 There is currently no available evidence for cardiovascular outcomes with weekly prolonged-release exenatide. Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) is a trial evaluating cardiovascular outcomes after treatment with weekly prolonged-release exenatide in patients with type 2 diabetes that is expected to complete in 2017.

7 Related NICE guidance

- [Liraglutide for the treatment of type 2 diabetes](#). NICE technology appraisal guidance 203 (2010).
- [Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes \(partial update of CG66\)](#). NICE clinical guideline 87 (2009).
- [Type 2 diabetes: the management of type 2 diabetes \(partially updated by CG87\)](#). NICE clinical guideline 66 (2008).
- [Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period](#). NICE clinical guideline 63 (2008). [Continuous subcutaneous insulin infusion for the treatment of diabetes \(review\)](#). NICE technology appraisal guidance 151 (2008).
- [Type 2 diabetes: prevention and management of foot problems](#). NICE clinical guideline 10 (2004).

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review at the same time as NICE technology appraisal 203 in May 2012. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon

Chief Executive

February 2012

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)

Consultant Physician, University Hospitals of Leicester

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Pamela Rees

Lay member

Dr Ann Richardson

Lay member

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr Mike Spencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

Mr David Thomson

Lay member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

Dr Luke Twelves

General Practitioner, Ramsey Health Centre, Cambridgeshire

Dr John Watkins

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Linda Landells and Kumar Perampaladas

Technical Leads

Eleanor Donegan

Technical Adviser

Bijal Joshi

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Waugh N, Cummins E, Shyangdan D, et al. Long-acting exenatide in the management of type 2 diabetes. A single technology appraisal. Warwick Evidence, August 2011

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Eli Lilly and Company

II Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- Diabetes UK
- National Diabetes Nurse Consultant Group
- National Obesity Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation
- UK Clinical Pharmacy Association (UKCPA)

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Bristol Myers Squibb
- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Merck Sharp & Dohme
- National Institute for Health Research Health Technology Assessment Programme
- Novo Nordisk
- Sanofi
- Warwick Evidence

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on exenatide prolonged-release suspension for injection by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Jiten Vora, Consultant Endocrinologist, nominated by organisation representing Eli Lilly and Company – clinical specialist
- Dr Peter Davies, Consultant Physician, nominated by organisation representing Association of British Clinical Diabetologists – clinical specialist

-
- Mrs Cathy Moulton, Clinical Advisor, nominated by organisation representing Diabetes UK–patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Eli Lilly and Company

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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