**Internal Clinical Guidelines Team**

# Appendix H: Deleted text appendix - Type 2 diabetes: newer agents

## Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes

*NICE short clinical guideline 87*

*Developed by the Centre for Clinical Practice at NICE*

*May 2009*

**The only recommendation being retained from this guideline is recommendation 3.2 within this version of the guideline or recommendation 1.6.3.2 in the NICE version of this guideline. This recommendation has been highlighted in yellow within this deleted text appendix.**

*This guideline will be stood down when the 2015 update publishes*

*Commissioned by the National Institute for Health and Clinical Excellence*

**This short clinical guideline partially updates NICE clinical guideline 66. The recommendations have been combined with unchanged recommendations from CG66 in NICE clinical guideline 87**

**September 2010**

In September 2010 the European Medicines Agency (EMA), the European Union (EU) body responsible for monitoring the safety of medicines, recommended the suspension of the marketing authorisation for rosiglitazone (Avandia, Avandamet and Avaglim) from GlaxoSmithKline. The EMA has concluded that the benefits of rosiglitazone no longer outweigh its risks and the marketing authorisation should be suspended across the EU.

The EMA has advised that patients who are currently taking rosiglitazone-containing medicines should make an appointment with their doctor at a convenient time to discuss suitable alternative treatments. Patients are advised not to stop their treatment without speaking to their doctor. NICE does not recommend the use of drugs without marketing authorisation. Therefore, as a result of the EMA's decision, NICE has temporarily withdrawn its recommendations on the use of rosiglitazone in this guideline.

**July 2011**

The Medicines and Healthcare products Regulatory Agency has issued new advice on the risk of bladder cancer with the anti-diabetic drug pioglitazone. Please refer to the advice at

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON123285

**NICE short clinical guideline 87**
**Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes**
**Ordering information**

You can download the following documents from www.nice.org.uk/CG87

- NICE clinical guideline 87– all the recommendations for the management of type 2 diabetes.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The NICE short clinical guideline (this document) and the full guideline for CG66 – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1863 (quick reference guide)
- N1864 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which 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, and informed by the summary of product characteristics of any drugs they are considering.

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 that would be inconsistent with compliance with those duties.

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# Contents

# Foreword

Type 2 diabetes is defined by high blood glucose and is characterised by an increased risk of problems including, among others, coronary, cerebrovascular, ophthalmological and renal disease. In addition to encouraging a healthy lifestyle and modifying levels of blood pressure and lipids, good care for people with diabetes includes lowering blood glucose in order to reduce the risk of complications. Blood glucose control is assessed by estimating plasma glucose and measuring haemoglobin A1c (HbA1c), which reflects control over the previous 2 to 3 months. High levels of HbA1c indicate the need for glucose-lowering drugs. With progression of type 2 diabetes over time multiple drugs, including insulin, are usually needed for good glycaemic control.

This guideline covers newer agents for blood glucose control in adults with type 2 diabetes; it does not address care for pregnant women with diabetes. It is a partial update of 'Type 2 diabetes', NICE clinical guideline 66 (CG 66, published in 2008). Specifically, this guideline updates and replaces recommendations in sections 1.6, 1.7.1.3, 1.7.2 and 1.7.3 of CG66. The new recommendations from this short guideline use the same levels of HbA1c for the addition of extra glucose-lowering drugs as defined in CG 66 (that is, a value of 6.5% for people on one glucose-lowering drug and 7.5% for people on two or more oral glucose-lowering drugs or people needing insulin). The use of these different levels takes into account the increasing risk of hypoglycaemia with insulin and the clinical and cost-effectiveness of the newer agents. Otherwise, CG 66 stands.

Other points to note are that:

- This guideline addresses only the licensed use of the included drugs.
- Exenatide is licensed as a drug to lower blood glucose in diabetes and not as a drug to promote weight loss.
- The use of long-acting insulin analogues is considered only in comparison with NPH insulin.
- With respect to the safety of thiazolidinediones, the recommendations in this guideline are fully consistent with the position of the regulatory bodies responsible for the safety of medicines (the European Medicines Agency the Medicines and Healthcare products Regulatory Agency) as of March 2009.
- As of March 2009, the following drugs and drug combinations had black triangle status: exenatide; pioglitazone; sitagliptin; vildagliptin; pioglitazone plus metformin; rosiglitazone plus metformin; vildagliptin plus metformin.
- The recommendations cover those drugs named in the scope and their licensed indications at the time (changes after September 2008 were not considered). They exclude liraglutide, which did not receive marketing authorisation for use in type 2 diabetes during the development of the guideline (December 2007 to May 2009). Similarly, these recommendations do not apply to drugs not yet available in the UK, nor do they incorporate methods of reporting $HbA_{1c}$ not currently in use in the UK.

For all drugs, recommendations are based on clinical and cost effectiveness and reflect whether their use for type 2 diabetes is a good use of NHS resources. This guideline should be used in conjunction with clinical judgment and decision-making appropriate for the individual patient.

# Patient-centred care

This guideline offers best practice advice on the care of adults with type 2 diabetes.

Treatment and care should take into account patients' needs and preferences. People with type 2 diabetes should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health (2001) guidelines – 'Reference guide to consent for examination or treatment' (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

# 1 Summary

## 1.1 List of all recommendations[a]

**1. DPP-4 inhibitors (sitagliptin, vildagliptin)**

1.1. Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

1.1.1. the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or

1.1.2. the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

1.2. Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

1.2.1. the person does not tolerate metformin, or metformin is contraindicated.

1.3. Consider adding sitagliptin[b] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[c].

1.4. Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).

1.5. Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.

1.6. A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if:

1.6.1. further weight gain would cause or exacerbate significant problems associated with a high body weight, or

1.6.2. a thiazolidinedione (pioglitazone, rosiglitazone) is contraindicated, or

1.6.3. the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone, rosiglitazone).

1.7. There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone, rosiglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference.

[a] Oral drugs are listed first.

b At the time of publication, sitagliptin was the only DDP-4 inhibitor with UK marketing authorisation for use in this combination.

c Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

## 2. Thiazolidinediones (pioglitazone, rosiglitazone)

2.1. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- 2.1.1. the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- 2.1.2. a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

2.2. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- 2.2.1. the person does not tolerate metformin or metformin is contraindicated.

2.3. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[d].

2.4. Do not commence or continue a thiazolidinedione (pioglitazone, rosiglitazone) in people who have heart failure, or who are at higher risk of fracture.

2.5. When selecting a thiazolidinedione (pioglitazone, rosiglitazone), take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost, safety and prescribing issues (see 1.1.13).

2.6. Only continue thiazolidinedione therapy (pioglitazone, rosiglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).

2.7. Consider combining pioglitazone with insulin therapy[e] for a person:

- 2.7.1. who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone, rosiglitazone), or
- 2.7.2. who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.

2.8. Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone, rosiglitazone) with the person to enable them to make an informed decision.

2.9. A thiazolidinedione (pioglitazone, rosiglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if:

- 2.9.1. the person has marked insulin insensitivity, or
- 2.9.2. a DPP-4 inhibitor (sitagliptin, vildagliptin) is contraindicated, or
- 2.9.3. the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor (sitagliptin, vildagliptin).

d Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

e At the time of publication pioglitazone was the only thiazolidinedione with UK marketing authorisation for use with insulin.

2.10. There may be some people for whom either a thiazolidinedione (pioglitazone, rosiglitazone) or a DPP-4 inhibitor (sitagliptin, vildagliptin) may be suitable and, in this case, the choice of treatment should be based on patient preference.

**3. GLP-1 mimetic (exenatide)**

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

3.1.1. a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

3.1.2. a BMI < 35.0 kg/m2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

3.2. Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

3.3. Discuss the potential benefits and risks of treatment with a GLP-1 mimetic (exenatide) with the person to enable them to make an informed decision.

**4. Insulin therapy**

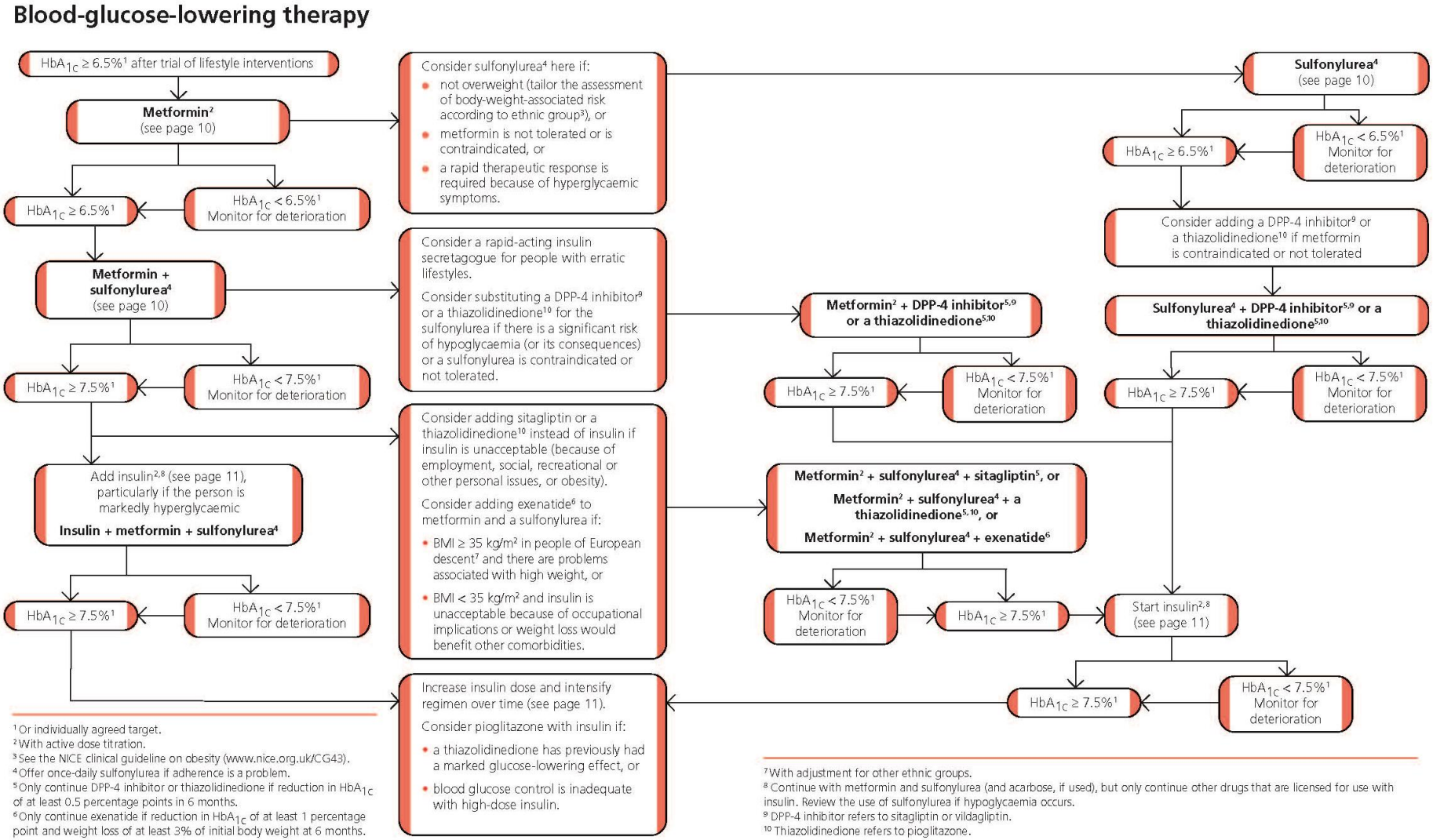
4.1. Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees.

4.2. For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification[f] not to.

4.3.

f Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

## 1.2 Care pathway



# 1.3 Overview

## 1.3.1 Use of newer agents for blood glucose control

Type 2 diabetes is a chronic metabolic disorder caused by relative insensitivity to insulin combined with insufficient insulin secretion. It is characterised by high levels of blood glucose (hyperglycaemia). If prolonged, hyperglycaemia can cause microvascular and macrovascular damage. Improving blood glucose levels, blood pressure and lipid levels delays or prevents the complications of diabetes. Current practice aims to achieve a glycated haemoglobin (HbA1c) level of 6.5%, or 7.5% for those at risk of severe hypoglycaemia, although healthcare professionals appreciate that these targets will not be achieved by everyone.

The prevalence of diagnosed diabetes approximates 3.7% in England and 4.2% in Wales. This equates to more than 2 million people, of whom more than 85% have type 2 diabetes. Diabetes is estimated to account for at least 5% of healthcare expenditure in the UK, and up to 10% of hospital budgets. Type 2 diabetes usually occurs in people older than 40 years; however, it can occur earlier, particularly in people of South Asian or African–Caribbean origin.

Although lifestyle interventions (diet and physical activity) are the first-line treatments for the management of type 2 diabetes, most people subsequently need sequential addition of oral glucose-lowering drugs. Metformin is widely used as first-line oral therapy, with the sulfonylureas added as second-line therapy if glycaemic control remains poor or deteriorates. Other oral drugs for lowering blood glucose include alpha-glucosidase inhibitors, thiazolidinediones and meglitinides. Because type 2 diabetes is progressive, with secretion of insulin decreasing over time, most people with type 2 diabetes eventually need insulin. Healthcare professionals can prescribe a variety of formulations of insulin, including long- or short-acting formulations, or a pre-mixed (biphasic) combination of short- and long-acting insulins.

In recent years new agents have been developed for blood glucose control. These include:

- DPP-4 inhibitors (sitagliptin and vildagliptin – also known as gliptins, or incretin enhancers)
- GLP-1 mimetics (exenatide – also known as incretin mimetics)
- long-acting insulin analogues (insulin detemir and insulin glargine).

In addition, there have been recent safety concerns on the use of thiazolidinediones (pioglitazone and rosiglitazone) for blood glucose control in type 2 diabetes.

This short clinical guideline aims to improve the care of adults with type 2 diabetes by making evidence-based recommendations on the place of these newer drugs for blood glucose control in the care pathway.

## 1.3.2 The NICE short clinical guideline programme

'Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes' (NICE short clinical guideline 87) is a NICE short clinical guideline. For a full explanation of the process, see www.nice.org.uk/guidelinesmanual.

## 1.3.3 Using this guideline

This document is for healthcare professionals involved in the management of people with type 2 diabetes. The target population is adults with type 2 diabetes. This guidance does not apply to pregnant women with diabetes.

This is the full version of the guideline. It is available from www.nice.org.uk/CG87. Printed summary versions of this guideline are available: 'Understanding NICE guidance' (a version for patients and carers) and a quick reference guide (for healthcare professionals). These are also available from www.nice.org.uk/CG87

## 1.354 Using recommendations and supporting evidence

The Guideline Development Group (GDG) reviewed the evidence (see section 4 and appendices 6.2 and 6.3). For each clinical question, the GDG was presented with a summary of the clinical and economic evidence, based on the studies reviewed and appraised. From this information the GDG derived the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in section 2.7 'Interpreting the evidence to make recommendations'.

# 2 Evidence review and recommendations

The most recent NICE guideline on the management of type 2 diabetes is 'Type 2 diabetes', NICE clinical guideline 66 (2008). It is a comprehensive guideline that covers the management of type 2 diabetes, including management of blood glucose, blood pressure and blood lipids. It makes recommendations relating to retinopathy and renal disease and on the use of oral glucose-lowering agents, including some of the newer agents included in this review. The current guideline updates only the recommendations in sections 1.6, 1.7.1.3, 1.7.2 and 1.7.3 of NICE clinical guideline 66. The recommendations from the current short clinical guideline have been combined with the unchanged recommendations from CG66 in NICE clinical guideline 87 (see www.nice.org.uk/CG87).

## 2.1 Newer agents for blood glucose control

### 2.1.1 Introduction

The four classes of drugs considered by the GDG are:

- the oral DPP-4 inhibitors, sitagliptin and vildagliptin
- the oral thiazolidinediones, pioglitazone and rosiglitazone, with respect to safety as well as clinical effectiveness
- the GLP-1 mimetic exenatide, which is given by injection twice daily
- the injectable long-acting insulin analogues, insulin detemir and insulin glargine.

This guideline makes recommendations on the use of these newer agents and their positions within the care pathway of control of blood glucose in people with type 2 diabetes.

These recommendations cover licensed indications only. The GDG recognised that changes to the licensed indications are likely to occur in future. Therefore, it is strongly recommended that prescribers consult the latest summary of product characteristics.

### 2.1.2 Overview of methods used

The review of the evidence, which comprised a systematic review of clinical and cost effectiveness with additional health economic modelling, was commissioned by NICE from the Technology Assessment Group based at the University of Aberdeen, see section 4.2.3.

The GDG used the review of the evidence to draft recommendations based on the best available evidence, following documented NICE processes. For a full description of the evidence review and the guideline process see section 4, 'Methods'.

## 2.2 DPP-4 inhibitors (sitagliptin, vildagliptin)

**1. DPP-4 inhibitors (sitagliptin, vildagliptin)**

**1.1. Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:**

1.1.1. the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or

1.1.2. the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

**1.2. Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:**

1.2.1. the person does not tolerate metformin, or metformin is contraindicated.

**1.3. Consider adding sitagliptin[7] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[8].**

**1.4. Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).**

**1.5. Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.**

**1.6. A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if:**

1.6.1. further weight gain would cause or exacerbate significant problems associated with a high body weight, or

1.6.2. a thiazolidinedione (pioglitazone, rosiglitazone) is contraindicated, or

1.6.3. the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone, rosiglitazone).

**1.7. There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone, rosiglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference.**

## 2.2.1 Introduction

Human GLP-1 has an extremely short half-life in the body. Dipeptidyl peptidase-4 breaks down GLP-1, so inhibiting this enzyme prolongs the activity of GLP-1. DPP-4 inhibitors are taken orally and, in general, are not associated with weight loss.

## 2.2.2 Evidence review

The evidence review is based on the executive summary of the technology assessment report. For full details, see appendix 6.2.

Reviewers identified trials in which a DPP-4 inhibitor (sitagliptin, vildagliptin) was used in combination therapy.

Only four published trials met the inclusion criteria (Bolli et al. 2008; Hermansen et al. 2007; Nauck et al. 2007b; Scott et al. 2008). Two compared dual therapy with a DPP-4 inhibitor plus metformin against a thiazolidinedione plus metformin (Bolli et al. 2008; Scott et al. 2008). One trial examined the effect of adding sitagliptin to dual therapy with metformin plus

7 At the time of publication, sitagliptin was the only DDP-4 inhibitor with UK marketing authorisation for use in this combination.

8 Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

a sulfonylurea (glimepiride) (Hermansen et al. 2007), and one evaluated the addition of sitagliptin to metformin compared with a sulfonylurea alone (Nauck et al. 2007b).

## 2.2.3 Evidence statements

The Cochrane review (Richter et al. 2008) provided summary evidence on adverse events and included all the studies reviewed here.

### 2.2.3.1 Key clinical question

What is the additional effect of adding a DPP-4 inhibitor to dual therapy compared with placebo?[9]

#### HbA1c

When sitagliptin[10] was added to metformin and a sulfonylurea (glimepiride),[11] HbA1c decreased by 0.59%[12] in the group receiving sitagliptin 100 mg once-daily (mean baseline HbA1c 8.27%) compared with an increase of 0.30% in the placebo group (mean baseline HbA1c 8.27%, between-group difference of 0.89%, 95% confidence interval [CI] 1.10 to 0.68, $p < 0.001$) at 24 weeks (Hermansen et al. 2007).

The GDG also considered the effect of adding a DPP-4 inhibitor to dual therapy with metformin or a sulfonylurea plus a thiazolidinedione. No relevant studies were identified.

#### Hypoglycaemia

When sitagliptin was added to metformin and a sulfonylurea (glimepiride), hypoglycaemia occurred within 24 weeks in 16.4% of the sitagliptin 100 mg once-daily group, compared with 0.9% of the placebo group (between-group difference of 15.5%, no confidence intervals reported, $p < 0.001$) (Hermansen et al. 2007).

#### Weight

When sitagliptin was added to metformin and a sulfonylurea (glimepiride), body weight increased by 0.4 kg at 24 weeks in the group receiving sitagliptin 100 mg once-daily (mean baseline 87.2 kg) compared with a decrease of 0.7 kg in the placebo group (mean baseline 86.7 kg, between-group difference of 1.1 kg, 95% CI 0.1 to 1.4, no p value reported) (Hermansen et al. 2007).

#### Quality of life

The included trial did not report any outcomes related to quality of life issues.

### 2.2.3.2 Key clinical question

What is the effect of using a DPP-4 inhibitor in combination with metformin when compared with a sulfonylurea added to metformin?[13]

9 Comparison 1e in the chapter on DPP-4 inhibitors in the technology assessment report, pp 64–80.
10 At the time of publication, sitagliptin was the only DDP-4 inhibitor with UK marketing authorisation for use in this combination.
11 Assessed as moderate quality, n = 441, follow-up 24 weeks.
12 Note that throughout this guideline percentage changes in HbA1c stated are percentage point changes, unless indicated otherwise.
13 Comparison 1a in the chapter on DPP-4 inhibitors in the technology assessment report, pp 64–80.

**HbA1c**

At 52 weeks, HbA1c decreased by 0.67% in the group randomised to receive sitagliptin 100 mg once-daily in addition to metformin (mean baseline HbA1c 7.52%) compared with a decrease of 0.67% in the group randomised to receive glipizide (sulfonylurea) as second-line therapy (maximum dose 20 mg/day; mean baseline HbA1c 7.48%, between-group difference of 0.01%, 95% CI 0.09 to 0.08, p = not significant) (Nauck et al. 2007b).[14]

**Hypoglycaemia**

Over 52 weeks, 4.9% of the group receiving sitagliptin 100 mg once-daily in addition to metformin experienced one or more hypoglycaemic episodes (50 episodes in 29 participants), compared with 32.0% of the group taking the sulfonylurea glipizide and metformin (657 episodes in 187 participants) (between-group difference of 27.1%, no CI or p value reported) (Nauck et al. 2007b).

**Weight**

At 52 weeks, body weight decreased on average by 1.5 kg in the group receiving sitagliptin 100 mg once-daily in addition to metformin (mean baseline 89.5 kg), compared with an increase of 1.1 kg in the group receiving glipizide (sulfonylurea) in addition to metformin (mean baseline 89.7 kg, between group difference of 2.5 kg, 95% CI 3.1 to 2.0, p < 0.001) (Nauck et al. 2007b).

**Quality of life**

The included trial did not report any outcomes related to quality of life.

### 2.2.2.3 Key clinical question

What is the effect of using a DPP-4 inhibitor in combination with a sulfonylurea when compared with a thiazolidinedione in combination with a sulfonylurea?[15]

No relevant studies were identified.

### 2.2.2.4 Key clinical question

What is the effect of using a DPP-4 inhibitor in combination with a thiazolidinedione when compared with a sulfonylurea in combination with a thiazolidinedione?[16]

No relevant studies were identified.

### 2.2.2.5 Key clinical question

What is the effect of using a DPP-4 inhibitor in combination with metformin when compared with a thiazolidinedione in combination with metformin?[17]

**HbA1c**

Two randomised controlled trials found no significant difference in the effect on HbA1c between a DPP-4 inhibitor and a thiazolidinedione when either was added to metformin.

14 Assessed as poor quality, n = 1172, follow-up of 52 weeks.
15 Comparison 1b in the chapter on DPP-4 inhibitors in the technology assessment report, pp 64–80.
16 Comparison 1c in the chapter on DPP-4 inhibitors in the technology assessment report, pp 64–80.
17 Comparison 1d in the chapter on DPP-4 inhibitors in the technology assessment report, pp 64–80.

Bolli and coworkers[18] reported a decrease in HbA1c of 0.88% when vildagliptin 50 mg twice daily was added to metformin (mean baseline HbA1c 8.4%), compared with 0.98% in the pioglitazone 30 mg/day group (mean baseline HbA1c 8.4%, between-group difference 0.10%, 95% CI 0.05 to 0.26, p = not significant) at 24 weeks (Bolli et al. 2008).

Scott and coworkers[19] reported a decrease in HbA1c of 0.73% when sitagliptin 100 mg once daily was added to metformin (mean baseline HbA1c 7.8%) compared with a decrease of 0.79% when rosiglitazone 8 mg once-daily group was added to metformin (mean baseline HbA1c 7.7%; between-group difference 0.06%, 95% CI 0.14 to 0.25, no p value reported) at 18 weeks (Scott et al. 2008).

**Hypoglycaemia**

Bolli and coworkers reported only one participant with mild hypoglycaemia in the vildagliptin and metformin group (n = 295) (Bolli et al. 2008).

Scott and coworkers reported no difference between the groups in the proportion of participants with hypoglycaemia (1% in both groups) (Scott et al. 2008).

**Weight**

Both randomised controlled trials found a statistically significant difference between the groups, with people in the thiazolidinedione groups gaining weight compared with a small change (gain or loss) in the DPP-4 inhibitor groups when these agents were added to metformin.

Bolli and coworkers reported an increase in body weight of 0.3 kg in trial participants when vildagliptin 50 mg twice daily was added to metformin (mean baseline 91.8 kg) compared with 1.9 kg when pioglitazone 30 mg/day was added to metformin (mean baseline 91.2 kg, between group-difference of - 1.6 kg, 95% CI - 2.2 to 1.0[20], p < 0.001) at 24 weeks (Bolli et al. 2008).

Scott and coworkers reported a decrease in body weight at 18 weeks of 0.4 kg when sitagliptin 100 mg once daily was added to metformin (mean baseline 83.1 kg) compared with a mean increase of 1.5 kg in the group receiving rosiglitazone 8 mg once daily (mean baseline 84.9 kg, between-group difference of - 1.9 kg, 95% CI - 2.5 to - 1.3) (Scott et al. 2008).

**Quality of life**

The trials did not report any outcomes related to quality of life.

### 2.2.326 Key clinical question

What is the effect of adding a DPP-4 inhibitor to dual oral therapy when compared with adding insulin to dual oral therapy?

In practice, when starting insulin, healthcare professionals would usually continue prescribing metformin and/or the sulfonlyurea and discontinue other oral agents, but this would depend on clinical circumstances.

Although only sitagliptin is currently licensed for this combination, relevant studies evaluating the effect of adding either sitagliptin or vildagliptin were searched for, and found none.

18 Assessed as moderate quality, n = 576, follow-up 24 weeks.
19 Assessed as moderate quality, n = 273, follow-up 18 weeks. It should be noted that the rosiglitazone arm was intended for 'estimation' purposes, rather than designed as a head-to-head trial.
20 Calculated from reported mean and standard error.

### 2.2.3.17 Key clinical question

What is the effect of adding a DPP-4 inhibitor to dual oral therapy compared with adding a thiazolidinedione to dual oral therapy?

Relevant studies evaluating the effect of adding either sitagliptin or vildagliptin to dual oral therapy were searched for. No studies were identified.

### 2.2.3.18 Key clinical question

What is the effect of adding a DPP-4 inhibitor to triple oral therapy when compared with insulin plus metformin?

Although the DPP-4 inhibitors are not currently licensed for this combination any relevant evidence was searched for, but no studies were found.

### 2.2.3.19 Outcomes overall

**Adverse effects**[21]

Generally, sitagliptin and vildagliptin were well tolerated.

Discontinuation because of adverse effects did not differ significantly between participants randomised to sitagliptin or vildagliptin intervention arms (range 1.7–3.1%, four studies) and those in control arms (range 0–3.6%, four studies). The risk ratios for the DPP-4 inhibitor groups and the control groups for serious adverse events were not statistically significantly different (risk ratios of 0.44 [Bolli et al 2008]; 0.76 [Hermansen et al 2007]; 0.97 [Nauck et al 2007]; 0.97 [Scott et al 2007]; overall risk ratio 0.97 [95% CI 0.75 to 1.27] for sitagliptin and 0.64 [95% CI 0.64 to 1.17] for vildagliptin) (Richter et al. 2008).

Although trials included in this review did not uniformly report rates of infection, one study (Scott et al. 2008) reported eight infections overall in the sitagliptin group (n = 94). Data from the Cochrane review (Richter et al. 2008) showed a small but significant increase in the rate of infection after sitagliptin treatment (relative risk [RR] 1.29, 95% CI 1.09 to 1.52, p = 0.003), but this was not increased after vildagliptin therapy (RR 1.04, 95% CI 0.87 to 1.24, p = 0.7).

No further relevant outcomes were reported.

## 2.2.3 Thiazolidinediones (pioglitazone, rosiglitazone)

**2. Thiazolidinediones (pioglitazone, rosiglitazone)**

**2.1. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:**

2.1.1. the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or

2.1.2. a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

**2.2. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood**

21 These are summary results from the Cochrane review based on all included studies.

**glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:**

2.2.1. the person does not tolerate metformin or metformin is contraindicated.

**2.3. Consider adding a thiazolidinedione (pioglitazone, rosiglitazone) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.[22]**

**2.4. Do not commence or continue a thiazolidinedione (pioglitazone, rosiglitazone) in people who have heart failure, or who are at higher risk of fracture.**

**2.5. When selecting a thiazolidinedione (pioglitazone, rosiglitazone), take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost, safety and prescribing issues (see 1.1.13).**

**2.6. Only continue thiazolidinedione therapy (pioglitazone, rosiglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).**

**2.7. Consider combining pioglitazone with insulin therapy[23] for a person:**

2.7.1. who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone, rosiglitazone), or

2.7.2. who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.

**2.8. Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone, rosiglitazone) with the person to enable them to make an informed decision.**

**2.9. A thiazolidinedione (pioglitazone, rosiglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if:**

2.9.1. the person has marked insulin insensitivity, or

2.9.2. a DPP-4 inhibitor (sitagliptin, vildagliptin) is contraindicated, or

2.9.3. the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor (sitagliptin, vildagliptin).

**2.10. There may be some people for whom either a thiazolidinedione (pioglitazone, rosiglitazone) or a DPP-4 inhibitor (sitagliptin, vildagliptin) may be suitable and, in this case, the choice of treatment should be based on patient preference.**

## 2.3.1 Introduction

The thiazolidinediones include pioglitazone and rosiglitazone. These oral drugs may be taken in combination with other oral agents or, in the case of pioglitazone, with insulin. They work by increasing the body's sensitivity to insulin. These drugs rarely cause hypoglycaemia, but commonly cause weight gain. They are associated with fluid retention (including peripheral oedema) and distal bone fractures (in women only).

22 Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

23 At the time of publication pioglitazone was the only thiazolidinedione with UK marketing authorisation for use with insulin.

## 2.3.2 Evidence review

For the thiazolidinediones, the GDG was interested in safety, particularly the risk of cardiovascular events. In addition, the GDG reviewed the evidence on the use of pioglitazone added to insulin.

## 2.3.3 Evidence statements

The clinical effectiveness of the thiazolidinediones has been previously evaluated by NICE. Details of the evidence reviewed can be found in 'Type 2 diabetes. National clinical guideline for management in primary and secondary care (update)' (see www.nice.org.uk/CG66FullGuideline).

### 2.3.3.1 Key clinical question

What is the additional effect of adding pioglitazone to an insulin?

**HbA1c**

A meta-analysis showed a statistically significant and clinically important lowering of HbA1c in the insulin-with-pioglitazone groups (eight studies) compared with the insulin-without-pioglitazone groups (weighted mean difference −0.5%, 95% CI −0.73 to −0.28) (Asnani et al. 2006; Berhanu et al. 2007; Fernandez et al. 2008; Mattoo et al. 2005; Raz et al. 2005; Rosenstock et al. 2002; Scheen and Charbonnel 2006; Shah et al. 2007).

**Hypoglycaemia**

There were significantly more participants with hypoglycaemic episodes in the groups receiving insulin with pioglitazone than in the groups receiving insulin without pioglitazone (RR 1.30, 95% CI 1.04 to 1.63, p = 0.02).

**Weight**

Participants in the pioglitazone-with-insulin groups tended to gain more weight (range of mean increases from 2.3 to 4.9 kg) than those in the insulin-alone groups (range of mean changes from 0.04 kg decrease to 2.4 kg increase).

**Other outcomes**

Reported withdrawals because of adverse events did not differ between the insulin-with-pioglitazone and the insulin-without-pioglitazone groups.

The only adverse event (apart from weight gain) reported as occurring more frequently with insulin plus pioglitazone was peripheral oedema, which was generally classified as mild to moderate. However, p values were generally not reported.

No data on congestive heart failure were reported in the included trials. For a more detailed discussion on adverse events associated with the use of thiazolidinediones, see below.

Insulin dose ranged between 42 and 64 U/day (0.5–1 U/kg per day) in the insulin-with-pioglitazone groups and between 55 and 70 U/day (0.7–1.2 U/kg per day) in the insulin-without-pioglitazone group.

**Blood lipid parameters**

Overall, the meta-analysis did not find any significant reduction in triglyceride levels for insulin with pioglitazone (weighted mean difference −0.34 mmol/litre, 95% CI −0.74 to 0.06, p = not significant) compared with insulin without pioglitazone.

Four studies reported total serum cholesterol. None found any significant difference in total cholesterol level between the insulin-with-pioglitazone and the insulin-without-pioglitazone groups.

Four studies reported high-density lipoprotein (HDL) cholesterol, and all found significantly increased values in the insulin-with-pioglitazone groups. Overall, HDL-cholesterol was increased by a weighted mean difference of 0.14 mmol/litre[24] (95% CI 0.09 to 0.19) in the insulin-with-pioglitazone groups.

Four studies reported low-density lipoprotein (LDL)-cholesterol. None found any significant difference between the insulin-with-pioglitazone and the insulin-without-pioglitazone groups.

### 2.3.3.2 Key clinical question

How safe are rosiglitazone and pioglitazone, and do their safety profiles differ?

The evidence on the effectiveness and the safety of the thiazolidinediones was reviewed and considered in 'Type 2 diabetes. National clinical guideline for management in primary and secondary care (update)' (see www.nice.org.uk/CG66FullGuideline). The aim of this update review was therefore to consider any evidence related to safety published more recently. For full details, see appendix 6.2.

In the short-term, the risks associated with rosiglitazone and pioglitazone include weight gain, fluid retention, peripheral oedema, expansion of plasma volume (contributing to a risk of anaemia and heart failure) and effects on lipid profiles.

Longer-term risks associated with rosiglitazone and pioglitazone include an increased risk of bone fractures in women. For rosiglitazone, there is a potentially increased risk of myocardial ischaemia based on meta-analysis of interventional trials (Diamond et al. 2007; Lago et al. 2007; Nissen and Wolski 2007; Psaty and Furberg 2007; Singh et al. 2007); pharmacoepidemiological studies show conflicting results. The risk of myocardial ischaemia and heart failure increase with concomitant insulin usage; rosiglitazone is not licensed for use with insulin. The available studies for pioglitazone, including published meta-analyses of trials (Jagger et al. 2003; Lincoff et al. 2007) and the completed long-term PROactive study (Dormandy et al. 2005), do not raise similar concerns about an increased risk of myocardial infarction in association with pioglitazone treatment. Observational studies differ in their conclusions about the associations between thiazolidinedione use and myocardial infarction or corsonary revascularisation.

These guidelines are fully consistent with the current regulatory position for these drugs from the Medicines and Healthcare products Regulatory Agency, which has responsibility for drug safety in the UK.

## 2.4 GLP-1 mimetic (exenatide)

**3. GLP-1 mimetic (exenatide)**

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

3.1.1. a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

24 Reported as a weighted mean difference of 5.43 mg/dl (95% CI 3.40 to 7.47) in the technology assessment report. Converted by dividing by 39.

3.1.2. a BMI < 35.0 kg/m2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

**3.2. Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).**

**3.3. Discuss the potential benefits and risks of treatment with a GLP-1 mimetic (exenatide) with the person to enable them to make an informed decision.**

## 2.4.1 Introduction

Exenatide is a GLP-1 mimetic (also described as an incretin mimetic); it increases insulin secretion, suppresses glucagon secretion and slows gastric emptying. Patients must inject exenatide twice daily.

## 2.4.2 Evidence review

The evidence review is based on the executive summary of the technology assessment report. For full details, see appendix 6.2.

The Technology Assessment Group searched for trials in which exenatide was added to dual therapy with metformin and a sulfonylurea when that combination failed to achieve adequate glycaemia control.

The GDG considered five randomised controlled trials (Davis et al. 2007; Heine et al. 2005; Kendall et al. 2005; Nauck et al. 2007a; Zinman et al. 2007) to be relevant and of reasonable quality. The main problems with quality included insufficient reporting of methods and failure to optimise comparator treatments. One trial randomised participants using insulin to use exenatide only or to continue with insulin (Davis et al. 2007). The GDG considered one other trial (Barnett et al. 2007; DeFronzo et al. 2005) which, although it did not meet the original criteria, provides data on metformin monotherapy compared with metformin plus exenatide. This trial was included at the request of the GDG to address the question of how to treat people whose weight was of considerable concern and in whom adding a sulfonylurea or a thiazolidinedione would cause undesirable further weight gain.

The GDG consider that one trial reviewed in the technology assessment report was not relevant to any of the clinical questions (Barnett et al. 2007). This is not included in the evidence statements and any further GDG discussions.

## 2.4.3 Evidence statements

### 2.4.3.1 Key clinical question

What is the additional effect of adding a GLP-1 mimetic (exenatide) to dual therapy when compared with placebo?[25]

#### HbA1c

Two randomised controlled trials[26] showed a statistically significant and clinically important decrease in HbA1c following the addition of exenatide to dual therapy.

Kendall and coworkers reported a decrease of 0.6% in HbA1c at 30 weeks when exenatide 5 micrograms twice daily was added to metformin and a sulfonylurea (mean baseline HbA1c

25 Comparison 1 in the chapter on GLP-1 mimetics in the technology assessment report, pp 36–63.
26 Kendall et al 2005 – assessed as moderate quality, n = 733, follow-up 30 weeks; Zinman et al 2007 – assessed as good quality, n = 233, follow-up 16 weeks.

8.5%), compared with 0.8% in the group receiving 10 micrograms of exenatide twice daily (mean baseline level HbA1c 8.5%) and an increase of 0.23% in the placebo group (mean baseline level HbA1c 8.5%, between group differences of −0.78% and −1.0% compared with placebo, no CI reported, $p < 0.0001$ for each group) (Kendall et al. 2005).

Zinman and coworkers reported a decrease in HbA1c of 0. 9% at 16 weeks when exenatide 10 micrograms twice daily was added to metformin and a thiazolidinedione,[27] (mean baseline HbA1c 7. 9%) compared with an increase of 0.1% in the placebo group (mean baseline HbA1c 7.91%, between group difference of 0.98%, 95% CI 1.21 to 0.74, $p < 0.001$) (Zinman et al. 2007).

**Hypoglycaemia**

Kendall and coworkers reported a higher incidence of hypoglycaemia in the group taking exenatide with metformin and a sulfonylurea (19.2% with exenatide 5 micrograms twice daily, 27.8% with exenatide 10 micrograms twice daily) compared with placebo (12.6%, between-group differences of 6.6% and 15.2% respectively compared with placebo, no CI or p value reported).

Zinman and coworkers reported no significant difference in the incidence of hypoglycaemia between the group taking exenatide with metformin and a thiazolidinedione and the placebo group (10.7% compared with 7.1%, between-group difference of 3.6%, 95% CI 4.6 to 11.8, p = not significant) (Zinman et al. 2007).

**Weight**

Both randomised controlled trials showed a small statistically significant decrease in weight with the addition of exenatide to dual therapy.

Kendall and coworkers reported decreases in body weight of 1.6 kg at 30 weeks when exenatide 10 micrograms daily was added to metformin and a sulfonylurea (mean baseline 97 kg) and 1.6 kg with the addition of exenatide 20 micrograms daily (mean baseline 98 kg), compared with 0.9 kg in the placebo group (mean baseline 99 kg, between-group differences of 0.7 kg for both groups compared with placebo, no CI reported, $p \leq 0.01$ for each group) (Kendall et al. 2005).

Zinman and coworkers reported a decrease in body weight of 1.8 kg at 16 weeks when exenatide 20 micrograms daily was added to metformin and a thiazolidinedione (mean baseline 97.5 kg), compared with 0.2 kg[28] in the placebo group (mean baseline 96.9 kg, between-group difference of 1.51 kg, 95% CI 2.15 to 0.88, $p < 0.001$) (Zinman et al. 2007).

**Quality of life**

The included trials did not report any outcomes related to quality of life.

Other reported outcomes

Zinman and coworkers reported no clinically important differences (details not given) in blood lipids and blood pressure (Zinman et al. 2007). Kendall and coworkers did not report any other outcomes (Kendall et al. 2005).

### 2.4.3.2 Key clinical question

What is the additional effect of adding a GLP-1 mimetic (exenatide) to metformin when compared with placebo? [29]

27 Approximately 20% of the participants were taking metformin as single therapy.
28 As read from figure 3 of the published paper. Between-group difference and confidence interval as reported.
29 Comparison 5 in the chapter on GLP-1 mimetics in the technology assessment report, pp 36–63.

**HbA1c**

DeFronzo and coworkers 2005[30] reported decreases in HbA1c of 0.4% at 30 weeks when exenatide 5 micrograms twice daily was added to metformin (mean baseline HbA1c 8.3%) and 0.78% with the addition of exenatide 10 micrograms twice daily (mean baseline HbA1c 8.2%), compared with an increase of 0.08% in the metformin-alone group (mean baseline HbA1c 8.2%, between-group differences of 0.48% and 0.88% respectively compared with placebo, no CI reported, $p < 0.002$ for each group) (DeFronzo et al. 2005).

**Hypoglycaemia**

DeFronzo and coworkers reported overall rates of mild-to-moderate hypoglycaemia of 4.5% over 30 weeks in the group that received exenatide 5 micrograms twice daily with metformin, and 5.3% in both the group that received exenatide 10 micrograms twice daily with metformin and the metformin-alone group (between-group differences of 0.8% and 0% respectively compared with placebo, no CI or p values reported) (DeFronzo et al. 2005).

**Weight**

DeFronzo and coworkers reported decreases in body weight of 1.6 kg at 30 weeks in the group that received exenatide 5 micrograms twice daily with metformin (mean baseline 100 kg) and 2.8 kg in the group that received exenatide 10 micrograms twice daily with metformin (mean baseline 101 kg), compared with 0.3 kg in the metformin-alone group (mean baseline 101 kg, between-group differences of 1.3 kg and 2.5 kg respectively compared with placebo, no CI reported, $p < 0.001$ for each group) (DeFronzo et al. 2005).

**Quality of life**

The included trials did not report any outcomes related to quality of life.

**Other reported outcomes**

DeFronzo and coworkers reported that exenatide treatment was not associated with an increased or decreased incidence of cardiovascular, hepatic or renal adverse events, but acknowledged that the studies were short term. Also, no differences in plasma lipids, laboratory safety parameters or blood pressure were observed between treatment arms. No further details on these outcomes were reported (DeFronzo et al. 2005).

### 2.4.2.3 Key clinical question

What is the additional effect of adding a GLP-1 mimetic (exenatide) to a thiazolidinedione and a sulfonylurea compared with placebo? [31]

No relevant studies were identified.

### 2.4.3.4 Key clinical question

What is the effect of adding a GLP-1 mimetic (exenatide) versus insulin to dual therapy (metformin and a sulfonylurea)?

What is the additional effect of adding a GLP-1 mimetic (exenatide) versus thiazolidinedione to dual therapy (metformin and a sulfonylurea)? [32]

30 Assessed as moderate quality, n = 733, follow-up 30 weeks.
31 Comparison 2 in the chapter on GLP-1 mimetics in the technology assessment report, pp 36–63.
32 Comparison 3 in the chapter on GLP-1 mimetics in the technology assessment report, pp 36–63.

When dual metformin and sulfonylurea therapy fails to achieve adequate glucose control, NICE clinical guideline 66 recommends the addition of a thiazolidinedione or insulin. These questions aim to answer whether healthcare professionals should offer a GLP-1 mimetic instead of insulin or a thiazolidinedione.

**HbA1c – comparison of a GLP-1 mimetic with insulin**

Two randomised controlled trials[33] showed no significant difference in HbA1c when exenatide was added instead of insulin glargine (Heine et al. 2005) or pre-mixed insulin with insulin aspart (Nauck et al. 2007a) to metformin and a sulfonylurea.

Heine and coworkers reported that HbA1c decreased by 1.11% at 26 weeks when exenatide 10 micrograms twice daily was added to metformin and a sulfonylurea (mean baseline HbA1c 8.18%). There was a similar decrease when insulin glargine was added to metformin and a sulfonylurea (mean baseline HbA1c 8.23%, between-group difference of 0.017%, 95% CI −0.123 to 0.157, p = not significant) (Heine et al. 2005).

Nauck and coworkers reported that HbA1c decreased by 1.04% when exenatide 10 micrograms twice daily was added to metformin and a sulfonylurea (mean baseline HbA1c 8.6%) compared with 0.89% in the pre-mixed insulin with insulin aspart group (mean baseline HbA1c 8.6%, between-group difference of −0.15%, 95% CI −0.32 to 0.01,p = 0.067) at 52 weeks (Nauck et al. 2007a).

No relevant studies comparing exenatide with insulins other than insulin glargine and pre-mixed insulin with insulin aspart were identified.

**HbA1c – comparison of a GLP-1 mimetic with a thiazolidinedione**

No relevant studies comparing the effectiveness of adding a thiazolidinedione or a GLP-1 mimetic (exenatide) to metformin and a sulfonylurea were identified.

**Hypoglycaemia**

Heine and coworkers reported that overall rates of hypoglycaemia were similar in both groups (7.3 episodes per patient-year in the group taking exenatide 10 micrograms twice daily with metformin and a sulfonylurea, compared with 6.3 episodes in the group taking insulin glargine with metformin and a sulfonylurea, between-group difference of 1.1 episode per patient-year, 95% CI −1.3 to 3.4, p = not significant). Nocturnal hypoglycaemia was less frequent (0.9 compared with 2.4 episodes per patient-year, between-group difference of −1.6, 95% CI −2.3 to −0.9) but daytime hypoglycaemia was more frequent (6.6 compared with 3.9 episodes per patient-year, between-group difference of 2.7, 95% CI 0.4 to 4.9) (Heine et al. 2005).

Nauck and coworkers reported lower overall rates (4.7 episodes per patient-year in the group taking exenatide 10 micrograms twice daily with metformin and a sulfonylurea, compared with 5.6 episodes in the group taking pre-mixed insulin with insulin aspart plus metformin and a sulfonylurea, between-group difference of −0.9, no CI or p value reported). Rates for nocturnal hypoglycaemia were significantly lower in the group taking exenatide with metformin and a sulfonylurea compared with the group taking pre-mixed insulin with insulin aspart plus metformin and a sulfonylurea (17% versus 25%, no CI reported, p < 0.038). The difference in rates of nocturnal hypoglycaemia was no longer significant when adjusted for mean baseline HbA1c (Nauck et al. 2007a).

33 Heine 2005 – assessed as moderate quality, n = 551, follow-up 26 weeks; Nauck 2007 – assessed as moderate quality, n = 505, follow-up 52 weeks.

Based on the two randomised controlled trials, effects on overall rates were mixed, but rates tended to be lower in the exenatide groups. Nocturnal hypoglycaemic episodes were consistently less frequent in the exenatide groups. Results for daytime rates were mixed.

#### Weight

Both trials showed a statistically significant greater weight loss in the exenatide groups compared with the insulin groups.

Heine and coworkers reported a decrease in body weight of 2.3 kg when exenatide 10 micrograms twice daily was added to metformin and a sulfonylurea (mean baseline 87.5 kg), compared with an increase of 1.8 kg in the insulin glargine group (mean baseline 88.3 kg, between-group difference of −4.1 kg, 95% CI −4.6 to −3.5, $p < 0.0001$) at 26 weeks (Heine et al. 2005).

Nauck and coworkers reported a decrease in body weight of 2.5 kg when exenatide 10 micrograms twice daily was added to metformin and a sulfonylurea (mean baseline 83.5 kg), compared with an increase of 2.9 kg in the pre-mixed insulin with insulin aspart group (mean baseline 83.4 kg, between-group difference of −5.4 kg, 95% CI −5.9 to −5.0, $p < 0.001$) at 52 weeks (Nauck et al. 2007a).

#### Quality of life

Subsequent publications from these two included trials reported outcomes related to quality of life, and these are discussed below (Secnik et al. 2006).

#### Other reported outcomes

Nauck and coworkers reported an increase in HDL-cholesterol both when exenatide 10 micrograms twice daily was added to metformin and a sulfonylurea and when pre-mixed insulin with insulin aspart was added to metformin and a sulfonylurea (between-group difference of −0.04 mmol/litre, 95% CI 0.06 to 0.02, $p = 0.003$).

Blood pressure fell (systolic by 5 mmHg; diastolic by 2 mmHg) with exenatide but did not change significantly with the use of pre-mixed insulin with insulin aspart (change of 1 mmHg for both systolic and diastolic, between-group differences of −4 mmHg and −3 mmHg respectively, no CI or p values reported) (Nauck et al. 2007a).

### 2.4.2.5 Key clinical question

What is the effect of replacing insulin with a GLP-1 mimetic (exenatide)? [34]

For some people with type 2 diabetes who are using insulin, it may be appropriate to stop insulin and try a GLP-1 mimetic. It should be noted that exenatide is not licensed for use with insulin.

One study was identified that aimed to explore the safety of substituting exenatide for insulin in people with type 2 diabetes using insulin in combination with oral glucose-lowering agents (Davis et al. 2007).

#### HbA1c

Davis and coworkers[35] reported no significant difference in HbA1c when exenatide 10 micrograms twice daily replaced the current (various) insulin regimens (increase of 0.3% in HbA1c in the exenatide group [mean baseline HbA1c 8.0%] compared with a decrease of

34 Comparison 4 the chapter on GLP-1 mimetics in the technology assessment report, pp 36–63.
35 Assessed as poor quality, n = 49, follow-up 16 weeks.

0.1% in the insulin group [mean baseline HbA1c 8.3%], between-group difference of 0.4%, no CI reported, p = not significant) at 16 weeks (Davis et al. 2007).

**Hypoglycaemia**

Davis and coworkers reported higher overall rates of hypoglycaemia (1.72 compared with 0.97 episodes per patient-year in the exenatide group and insulin groups respectively; between-group difference of 0.75 episodes per patient-year, no CI or p value reported), with most episodes occurring in the daytime. Of the 13 people taking exenatide who reported hypoglycaemia, 10 were also taking a sulfonylurea (Davis et al. 2007).

**Weight**

Davis and coworkers reported a statistically significant greater weight loss at 16 weeks in the exenatide 10 micrograms twice-daily group compared with the insulin group (decrease of 4.2 kg in the exenatide group from a mean baseline of 95 kg, compared with an increase of 0.5 kg in the insulin group from a mean baseline of 102 kg, between-group difference of 4.7 kg, no CI reported, $p < 0.001$) (Davis et al. 2007).

**Quality of life**

The included trial did not report any outcomes related to quality of life.

### 2.4.3.6 Overall outcomes

**Nausea and vomiting**

All randomised controlled trials reported a high frequency of nausea with exenatide (range 33.2–57.1%, seven studies), with vomiting not uncommon (range 9.6–17.4%, six studies). The number of participants who had to stop exenatide because of side effects was lower (range 5.7–16%, four studies).

Most nausea was mild, and the frequency decreased over time. DeFronzo and coworkers reported a rate of nausea[36] of 25–30% for the first 8 weeks in the group receiving exenatide 10 micrograms twice daily with metformin, reducing to approximately 12% by 28 weeks (DeFronzo et al. 2005). A decline in the proportion of participants experiencing nausea was also noted in the group receiving exenatide 5 micrograms twice daily with metformin, with initial rates of 15–25% falling to approximately 10% by 28 weeks (DeFronzo et al. 2005). Heine and coworkers found that 55% of people reported nausea in the first 8 weeks, compared with 13% in weeks 18–26 (Heine et al. 2005). Kendall and coworkers reported rates of approximately 30% in the first 8 weeks, compared with fewer than 10% in weeks 24–28 (Kendall et al. 2005). Zinman and coworkers had 41 reports of nausea in week 8, compared with 19 reports in week 16 (assumed to be in the exenatide with thiazolidinedione group, n = 121, calculated rates of 34% and 16% respectively). Nausea was described as mild in 44% of participants and as moderate in 40% (Zinman et al. 2007).

**Pancreatitis**

No study reported on the development of pancreatitis or the measurement of amylase.

### 2.4.3.7 Quality of life

Subsequent reports from two trials stated the following:

- No statistically significant differences for EQ–5D, the vitality scale of the SF–36, the Diabetes Symptom Checklist and the Diabetes Treatment Satisfaction Questionnaire were

36 Assumed to be 'all nausea' but not specified.

seen between the exenatide group and the group receiving insulin glargine (Secnik et al. 2006).

- Using EQ–5D and SF–36, participants in the exenatide group showed an improvement in quality of life, whereas those in the group receiving pre-mixed insulin with insulin aspart showed no change (Yurgin et al. 2006).

# 2.5 Long-acting human insulin analogues

**4. Long-acting human insulin analogues**

**4.1. Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees.**

**4.2. For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification[37] not to.**

**4.3. When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:**

4.3.1. structured education

4.3.2. continuing telephone support

4.3.3. frequent self-monitoring

4.3.4. dose titration to target

4.3.5. dietary understanding

4.3.6. management of hypoglycaemia

4.3.7. management of acute changes in plasma glucose control

4.3.8. support from an appropriately trained and experienced healthcare professional.[38]

**4.4. Initiate insulin therapy from a choice of a number of insulin types and regimens.**

4.4.1. Begin with human NPH insulin injected at bed-time or twice daily according to need.

4.4.2. Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:

4.4.3. the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or

4.4.4. the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or

4.4.5. the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or

4.4.6. the person cannot use the device to inject NPH insulin.

37 Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

38 This recommendation is from NICE clinical guideline 66.

4.4.7. Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA1c ≥ 9.0%). A once-daily regimen may be an option.

4.4.8. Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:

4.4.9. a person prefers injecting insulin immediately before a meal, or

4.4.10. hypoglycaemia is a problem, or

4.4.11. blood glucose levels rise markedly after meals.

**4.5. Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people:**

4.5.1. who do not reach their target HbA1c because of significant hypoglycaemia, or

4.5.2. who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or

4.5.3. who cannot use the device needed to inject NPH insulin[39] but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or

4.5.4. who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.

**4.6. Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue [insulin detemir, insulin glargine]) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).**

**4.7. Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or long-acting insulin analogues (insulin detemir, insulin glargine), if blood glucose control remains inadequate.**

## 2.5.1 Introduction

Insulin detemir and insulin glargine are long-acting human insulin analogues. They are prepared by modifying human insulin to change its solubility. This allows slow release into the bloodstream from subcutaneous tissue and a longer duration of action, which more closely mimics natural basal insulin secretion.

Both insulin detemir and insulin glargine are administered via subcutaneous injection and are licensed for use with oral glucose-lowering agents.

## 2.5.2 Evidence review

The evidence review is based on the executive summary of the technology assessment report. For full details, see appendix 6.2.

Several published systematic reviews were identified, and were updated with new published trials. Three reviews (Horvath et al. 2007; Tran et al. 2007; Warren et al. 2004) assessed as being of good quality were included; the reviews included 14 trials of insulin glargine and two of insulin detemir. Three new trials (Montanana et al. 2007; Pan et al. 2007; Philis-Tsimikas et al. 2006) (one of insulin glargine and two of insulin detemir) were combined with the

39 See NICE clinical guideline 87.

relevant older ones in updated meta-analyses. One trial of insulin glargine versus insulin detemir was also included (Rosenstock et al. 2008).

## 2.5.3 Evidence statements

### 2.5.3.1 Key clinical question

Does the effectiveness differ between NPH insulin and a long-acting insulin analogue (insulin glargine, insulin detemir) when a basal insulin is indicated?[40]

In type 2 diabetes, healthcare professionals suggest treatment with insulin when a combination of oral drugs, diet and physical activity do not adequately control blood glucose. Usual practice is to add basal insulin to metformin and other oral therapies as appropriate.

**HbA1c**

A meta-analysis showed no statistically significant differences in HbA1c between insulin glargine (ten studies) or insulin detemir (four studies) compared with NPH insulin.

Overall, both insulin glargine and NPH insulin effectively lower HbA1c: no significant difference was seen between the insulins (mean difference 0.00% HbA1c, 95% CI −0.11 to 0.10).

Overall, both insulin detemir and NPH insulin effectively lower HbA1c: no significant difference was seen between the insulins (mean difference 0.07% HbA1c, 95% CI −0.03 to 0.18).

**Hypoglycaemia**

A meta-analysis showed statistically significant lower rates of any hypoglycaemia with insulin glargine (seven studies) or insulin detemir (four studies) compared with NPH insulin.

Overall, fewer participants reported any hypoglycaemia in the insulin glargine groups (range 23.8–62.3%) than in the NPH insulin groups (range 32.4–74.6%; relative risk [RR] 0.89; 95% CI 0.83 to 0.96).

Overall, fewer participants reported any hypoglycaemia in the insulin detemir groups (range 16.0–63.7%) than in the NPH insulin groups (range 32.3–80.3%; RR 0.68; 95% CI 0.54 to 0.86).

Overall (four studies), fewer participants reported symptomatic hypoglycaemia in the insulin glargine groups (range 27.2–61.4%) than in the NPH insulin groups (range 48.5–66.8%; RR 0.80; 95% CI 0.68 to 0.93).

A meta-analysis showed no statistically significant difference for the rates of severe hypoglycaemia between insulin glargine (six studies) and insulin detemir (four studies) compared with NPH insulin.

Overall, the numbers of participants with severe hypoglycaemia were similar in the insulin glargine groups (range 0–2.6%) and NPH insulin groups (range 0–4.4%; RR 0.82; 95% CI 0.45 to 1.49).

Overall, the numbers of participants with severe hypoglycaemia were similar in the insulin detemir (range 0.4–1.8%) and NPH insulin groups (range 0–2.5%; RR 0.59; 95% CI 0.15 to 2.24).

40 Comparisons 1–4 in the chapter on long-acting insulin analogues in the technology assessment report, pp81–146.

A meta-analysis showed statistically significant lower rates of nocturnal hypoglycaemia with insulin glargine (seven studies) or insulin detemir (four studies) than with NPH insulin.

Overall, the numbers of participants with nocturnal hypoglycaemia were lower in the insulin glargine groups (range 7.4–31.3%) than in the NPH insulin groups (range 23.8–40.2%; RR 0.54; 95% CI 0.43 to 0.69).

Overall, the numbers of participants with nocturnal hypoglycaemia were lower in the insulin detemir groups (range 4.7–30.0%) than in the NPH insulin groups (range 13.4–47.1%; RR 0.54; 95% CI 0.42 to 0.68).

**Weight**

The range of weight change for participants in the insulin glargine group compared to the NPH group was a loss of 1.1kg to a gain of 0.3kg (median weight loss of 0.1kg), and for participants in the detemir group compared to the NPH group the range was a loss 1.6kg to a loss of 0.8kg (median weight loss 1.2kg). Meta-analyses could not be carried out because of a lack of data.

**Quality of life**

The included trials did not report enough details related to quality of life to draw meaningful conclusions.

### 2.5.132 Overall outcomes

**Adverse events**

Three trials reported adverse events:

- One study reported 66 adverse events (in 45 participants) that were possibly related to treatment (22 participants in the insulin glargine group; 23 in the NPH insulin group). Injection-site reactions accounted for most, and although p values were not reported, there appeared to be no significant difference between groups. There was no significant difference in serious adverse events between groups, and no events were considered not related to the treatment (Pan et al. 2007).
- In the PREDICTIVE-BMI trial, there were 91 adverse events in the insulin detemir group and 73 in the NPH insulin group, six of these in the insulin detemir group and four in the NPH insulin group were serious (but thought to be unlikely to be related to basal insulin). There were three withdrawals because of adverse events in the insulin detemir group and none in the NPH insulin group. (Montanana et al. 2007)
- In the third study, there was no statistically significant difference in the incidence of adverse events between comparison groups (150 events in 70 participants who received evening insulin detemir, 144 events in 82 participants who received NPH insulin). No serious adverse events were considered to be related to the insulins. There was no statistically significant difference in potential allergic reactions[41] (five events in five participants who received evening insulin detemir, one event in one participant who received NPH insulin) or injection-site reactions (seven events in six participants who received evening insulin detemir, two events in two participants who received NPH insulin) between the groups (Philis-Tsimikas et al. 2006).

However, no data were available on the longer-term safety of the insulin analogues. Nor was information available on complications of diabetes, and the studies were underpowered to reliably assess these outcomes.

41 As described in the paper – no further details reported.

**Total daily dose of insulin**

There were no statistically significant differences in mean daily insulin doses between treatment groups reported in two trials (Pan et al. 2007; Philis-Tsimikas et al. 2006).

### 2.5.343 Key clinical question

What is the effect of using insulin glargine compared with insulin detemir?[42]

**HbA1c**

Rosenstock and coworkers[43] reported that there were no significant differences in HbA1c between insulin detemir and insulin glargine; both reduced HbA1c by approximately 1.5% at 52 weeks (mean baseline HbA1c 8.62% and 8.64% in the insulin detemir and insulin glargine groups respectively; between-group difference of 0.05%, 95% CI −0.11 to 0.21) (Rosenstock et al. 2008).

**Hypoglycaemia**

Overall reported rates of hypoglycaemic episodes or nocturnal hypoglycaemic episodes were similar in both groups (overall rates per patient-year of 6.2 and 5.8 in the insulin detemir and insulin glargine groups respectively; RR 0.94, 95% CI 0.71 to 1.25; nocturnal rates per patient-year of 1.3 in both the insulin detemir and insulin glargine groups; RR 1.05, 95% 0.69 to 1.58) (Rosenstock et al. 2008).

**Weight**

Participants randomised to insulin detemir gained less weight at 52 weeks (2.7 kg increase from mean baseline of 87.4 kg) than those randomised to insulin glargine (3.5 kg increase from mean baseline of 87.4 kg) (between-group difference of −0.8 kg, no CI reported, p = 0.03) (Rosenstock et al. 2008).

Participants who administered insulin detemir once daily gained less weight at 52 weeks (mean 2.3 kg) than participants who administered insulin detemir twice daily (mean 3.7 kg, similar to that seen with insulin glargine) (Rosenstock et al. 2008).

**Quality of life**

The included trial did not report any outcomes related to quality of life.

**Other outcomes**

Mean daily dose was higher for insulin detemir (0.52 U/kg with once-daily dosing; 1.00 U/kg with twice-daily dosing) than for insulin glargine (0.44 U/kg with once-daily dosing).

Injection-site reactions were more common with insulin detemir than with insulin glargine (4.5% versus 1.4%, between group difference of 3.1%, no CI or p value reported).

## 2.6 Cost effectiveness

### 2.6.1 Published studies

The Assessment Group undertook a systematic review of relevant cost and cost-effectiveness studies. The review also considered evidence published in abstracts. The

42 Comparison 5 in the chapter on long-acting insulin analogues in the technology assessment report, pp81–146.
43 Assessed as of good quality, n = 582, follow-up 52 weeks.

majority of the studies identified by the Assessment Group were not UK based, and many were sponsored by drug manufacturers. Unless otherwise stated, the following summary focuses on full economic evaluations undertaken from a UK perspective. For details of the other identified studies, refer to the technology assessment report, appendix 6.2. Note that the Assessment Group also included in their review consideration of some relevant assessments undertaken by the Scottish Medicines Consortium.

#### 2.6.171 Exenatide versus glargine

In a manufacturer-sponsored study, Ray and coworkers compared exenatide with insulin glargine using the diabetes model originally developed by the Center for Outcomes Research – the CORE model (Ray et al. 2007).[44] The base-case cost of exenatide was drawn from the US cost converted at the prevailing exchange rate, because the UK acquisition cost was unavailable at the time of the analysis. The cost year of the analysis was 2004. Utility gains from weight loss were applied to the first 2 years of the simulations; values were taken from Cost of Diabetes in Europe – Type 2 (CODE-2) data that jointly analysed the effect of nausea and BMI.[45] After 2 years, a utility loss of 0.0061 per unit of BMI above 25 kg/m2 was applied (as derived from CODE-2 time trade-off data as analysed by Bagust and Beale 2005). Costs and benefits were discounted at 3.5% annually.

In the base case, the model simulated expected benefits and costs over a 35-year time horizon. Exenatide was both more effective and more costly than insulin glargine; the estimated incremental cost-effectiveness ratio (ICER) was £22,420 per quality-adjusted life year (QALY). These results were sensitive to the assumed utility gain from weight loss: using CODE-2 utilities elicited using time trade-off for the weight gain increased the ICER to £39,763.

A second study was identified that compared exenatide with insulin glargine from a UK perspective. The analysis (Woehl et al. 2008) (which was sponsored by the manufacturer of insulin glargine) was based on a discrete event simulation model of people with type 2 diabetes using risk functions derived from the UK Prospective Diabetes Study (UKPDS) for the development of vascular complications and a multivariate regression for the utility decrement associated with hypoglycaemia. The model simulated a cohort of 1000 people over a 40-year time horizon. These people had similar baseline characteristics to those used in the 2007 study of Ray and coworkers (Ray et al. 2007). The results indicate that exenatide is not cost effective: insulin glargine was found to be both less costly and more effective than exenatide in all modelled scenarios.

Differences between these two studies appear to be related in part to certain inputs used in the model. For example, the study by Woehl and coworkers (Woehl et al. 2008) did not include any potential disutility associated with weight gain.

#### 2.6.172 Insulin glargine and insulin determir

The study by McEwan and coworkers (which was funded by the manufacturer of insulin glargine) compared the use of insulin glargine with NPH insulin (McEwan et al. 2007). The study used a discrete event simulation model to forecast costs and health outcomes of a cohort of 1000 people over a 40-year time horizon. Prices were in Pounds Sterling at 2005 costs. Costs and benefits were discounted at 3.5% per year. This study showed insulin glargine to be highly cost effective for the two scenarios modelled: in a scenario based on differences in hypoglycaemia only, the ICER was approximately £10,000 per QALY; in the scenario based on differences in HbA1c only, the ICER was approximately £14,000 per

44 The CORE model is an internet-based interactive computer simulation that forecasts the long-term health outcomes and economic consequences of type 1 and type 2 diabetes.

45 CODE-2 is a cross-sectional study of people with type 2 diabetes. The study involved eight European countries, including the UK. A sub-study was carried out in five of these eight countries, with nearly 4800 participants completing the EuroQol EQ–5D.

QALY. The Assessment Group noted that the relative reduction in hypoglycaemia used in the model was 40%, based on a meta-analysis carried out by the manufacturer. However, the baseline rate of hypoglycaemia was based partly on studies in type 1 diabetes and is therefore not be relevant to people with type 2 diabetes, who have much lower rates of hypoglycaemia.

The Assessment Group identified one full paper evaluating the cost effectiveness of insulin detemir (Valentine et al. 2007). The manufacturer of the drug sponsored the study, and the perspective was that of the US healthcare system. This evaluation was based on the CORE model and compared the use of insulin detemir with oral glucose-lowering agents, NPH insulin and insulin glargine. Data inputs were informed by the results of PREDICTIVE, an observational study. Over a 35-year time horizon, insulin detemir was highly cost effective compared with the alternatives: the base-case ICERs were less than US$7,500; however, the Assessment Group questioned whether the estimates of clinical effectiveness used in the model overly favoured insulin detemir, because it assumed that HbA1c was 0.6% lower on detemir than on glargine or NPH.

Another full paper examining the cost-effectiveness of insulin detemir has since been identified. This analysis by Valentine and coworkers (2008) took the perspective of the German healthcare system. It aimed to evaluate the long-term cost-effectiveness of transferring people with type 2 diabetes to an insulin detemir regimen when control was inadequate with oral antidiabetic agents alone, or in combination with NPH insulin, or with insulin glargine. As in the earlier study (Valentine et al. 2007), the modelling was based on findings from a German subanalysis of the PREDICTIVE study and was sponsored by the manufacturer of insulin detemir. The authors concluded that conversion to insulin detemir with or without oral antidiabetic agents in people in whom control was inadequate with oral agents alone, or in combination with NPH or insulin glargine, was associated with improvements in life expectancy, quality-adjusted life expectancy and cost savings in the three scenarios evaluated.

A UK NHS-relevant cost-effectiveness analysis of insulin detemir was identified but was available only as an abstract. Using the CORE model, Smith and coworkers estimated the cost effectiveness of insulin detemir compared with NPH insulin basal bolus in people with type 2 diabetes. The modelling estimated an ICER of £19,218 per QALY for insulin detemir relative to NPH insulin (Smith et al. 2004).

#### 2.6.133 Sitagliptin and vildagliptin versus rosiglitazone and pioglitazone

The modelling study of Schwarz and coworkers aimed to assess the cost effectiveness of sitagliptin in the context of six European countries: Austria, Finland, Portugal, Scotland, Spain and Sweden (Schwarz et al. 2008). The analysis used the Januvia Diabetes Economic (JADE) model, which relies extensively on the UKPDS Outcomes Model risk equations.

Schwartz and coworkers explored the cost effectiveness of adding second-line sitagliptin for people with uncontrolled hyperglycaemia (defined as an HbA1c rising above 6.5%) on a regimen of metformin. For the UK modelling based on Scottish data, the estimated ICER of sitagliptin versus rosiglitazone was £1567 per QALY. For the comparison with the sulfonylurea, in which people who did not respond progressed to insulin, the estimated ICER was £8045 per QALY. For the comparison with the sulfonylurea, in which people who did not respond progressed to rosiglitazone plus metformin prior to insulin, the ICER was £7502.

In all sensitivity analyses, sitagliptin remained highly cost effective (ICERs were well below a threshold of £20,000 per QALY).

The Assessment Group noted a limitation of this study in that it considered sitagliptin as a second-line therapy rather than as a third-line addition to metformin and sulfonylurea.

The Assessment Group did not identify any papers that considered the cost effectiveness of vildagliptin from a UK NHS perspective. Two abstracts (Fon et al. 2007) and (Celeya et al. 2007) were identified that compared the relative cost effectiveness of sitagliptin, vildagliptin, rosiglitazone and pioglitazone from the perspective of the Mexican healthcare system. Outcome measures in these studies were unclear, but appeared to be simply a per-unit reduction of HbA1c. Both abstracts concluded that vildagliptin dominated other treatments.

De novo analysis in 'Type 2 diabetes. National clinical guideline for management in primary and secondary care (update)'

A de novo cost-effectiveness analysis of third-line treatment regimens, based on the UKPDS Outcomes Model was presented in 'Type 2 diabetes. National clinical guideline for management in primary and secondary care (update)' (see www.nice.org.uk/CG66FullGuideline). The UKPDS Outcomes Model is a computerised simulation, designed to estimate life expectancy, quality-adjusted life expectancy and costs of complications in people with type 2 diabetes. It uses the equations and algorithms published in the UKPDS.

The analysis undertaken for NICE clinical guideline 66 compared the following treatment alternatives: NPH insulin, pre-mixed insulin analogues, insulin glargine, pioglitazone and rosiglitazone, and exenatide. Human NPH insulin was found to be the most cost-effective option in the base case. It remained the most cost-effective option in different subgroups when one characteristic of the population was changed at a time. It also remained the most cost-effective option if it was assumed that the treatment effect of all the therapies lasted for 10 years instead of 3 years.

It is important to note that NICE clinical guideline 66 also considered the cost-effectiveness evidence relating to the use pioglitazone and rosiglitazone as second-line therapy.

### 2.6.2 De novo cost-effectiveness analysis for this guideline on newer agents

The Assessment Group also undertook a de novo cost-effectiveness analysis of the various regimens using the UKPDS Outcomes Model. The baseline characteristics applied in the modelling were based on those used in 'Type 2 diabetes. National clinical guideline for management in primary and secondary care (update)' (see www.nice.org.uk/CG66FullGuideline). The base case therefore assumed, for example, a starting age of 58 years and a BMI of 30 kg/m2. Men and women were modelled separately. Because women are on average slightly shorter than men, for a given BMI the average female patient weight is slightly less. The baseline weight for men in the model was 87 kg; for women it was 82 kg.

Analyses were undertaken with or without inclusion of background prevalence of various complications based on The Health Improvement Network, THIN study (RTI Health Solutions, 2006). The 'with complications' analysis assumed that people with one complication would not have another concurrently. The Assessment Group presented cost-effectiveness results for pair-wise comparisons based on evidence from head-to-head clinical trials, as identified in the clinical effectiveness review. In initial modelling, an attempt was made to consider the cost effectiveness of comparisons for which no direct head-to head data exists. These data are not presented in the final version of the Assessment Group's report or the current Guideline because of concerns about the appropriateness of undertaking indirect treatments analyses in this instance.

The pair-wise comparisons were as follows:

- exenatide versus insulin glargine
- sitagliptin versus rosiglitazone
- vildagliptin versus pioglitazone
- insulin glargine versus NPH insulin

- insulin detemir versus NPH insulin.

The Assessment Group noted that because the UKPDS Outcomes model is a patient-level simulation, a number of iterations of the model have to be performed in order to reduce the variability in the estimates of cost-effectiveness obtained. For this reason, and taking account computational constraints, the Assessment Group performed 250,000 iterations of the model for each estimate of expected cost-effectiveness. The Assessment Group did not make use of the ability of the UKPDS Outcomes model to characterise second-order uncertainty, that is, uncertainty related to precision of mean parameter values. The reasons for this are given in the technology assessment report (appendix 6.2).

The perspective taken was that of the NHS and UK personal social services, and the analysis had a 40-year time horizon. In estimating drug treatment costs, the analysis took into account the fact that insulin doses are weight dependent. In addition, the analysis attempted to account for the costs of pens, needles and nurse specialist time needed to support people with diabetes who are starting insulin therapy. Both costs and benefits were discounted at an annual rate of 3.5%. Drug acquisition costs were sourced from the 'British national formulary' (BNF) 56 (September 2008).

The absolute impacts on HbA1c, weight, cholesterol and systolic blood pressure of the interventions considered in the analysis were applied as an initial treatment, and the UKPDS Outcomes Model was run to predict the evolution of HbA1c. The analysis assumed that treatment would be intensified if the 7.5% HbA1c threshold was reached. The UKPDS Outcomes model suggests that there would be a progressive upward drift in HbA1c despite any initial reductions as a result of treatment. Although non-insulin regimens postpone the need for insulin, they do not prevent it. It was therefore assumed that a requirement for further glucose-lowering therapy would involve starting an insulin preparation.

To analyse the direct utility impact of weight gain/loss and severe hypoglycaemia, the survival curves of the UKPDS Outcomes Model were used to append these effects to the estimates of costs and QALYs.

It was assumed that there would be a quality of life increment of about 0.006 for a 3% weight loss/gain and an increment of 0.010 for a 5% weight loss/gain. The QALY loss from nausea associated with the use of exenatide was assumed to be 0.012.

The base-case analysis assumed a 0.01 utility gain from the reduced fear associated with a reduction in severe hypoglycaemic episodes. The baseline rate of severe hypoglycaemic episodes was assumed to be 0.35 per patient-year. For the comparison of glargine versus NPH, it was assumed that glargine would lead to fewer severe hypoglycaemic episodes with an associated relative risk of 0.82. In the case of the comparison between insulin detemir and NPH, it was also assumed that detemir would lead to fewer episodes of hypoglycaemia – the relative risk applied in this instance was 0.59. The differences in severe hypoglycaemia on which these relative risk point estimates are based were not statistically significant (see section 2.5.3).

Because of the unavailability of appropriate source data, the possible impact of treatment on nocturnal hypoglycaemic episodes was not modelled directly. However, the Assessment Group argued that a proportion of the impact of nocturnal hypoglycaemia on health-related quality of life will be captured via the reduction in severe hypoglycaemic episodes.

#### 2.6.241 Comparisons based on pair-wise head-to-head evidence

**Exenatide versus insulin glargine**

In the comparison of exenatide with insulin glargine, it was assumed that insulin glargine was cost effective. The analysis therefore assumed that when eventual insulin therapy was necessary, this would involve the use of insulin glargine. Although the evidence appears to

suggest there may be a small risk of developing pancreatitis as a result of exenatide treatment, this was not considered in the modelling.

In the analysis, exenatide in combination with metformin and a sulfonylurea was compared with insulin glargine in combination with metformin and a sulfonylurea.

The model incorporated an initial weight loss effect of exenatide therapy of 2.3 kg and an initial weight gain effect associated with glargine of 1.8 kg. (Heine et al. 2005).

Two scenarios were modelled. In the first scenario, it was assumed that the change in HbA1c associated with initial insulin glargine therapy may be less rapid than that associated with treatment with exenatide. This is because exenatide is administered as a fixed dose, whereas the insulin glargine dose needs to be titrated. In the second scenario, it was assumed that changes in HbA1c over time slightly favour exenatide.

In the first scenario, for men with a starting BMI of 30 kg/m2, exenatide was associated with greater expected benefit in terms of QALYs compared with insulin glargine, although exenatide was also more expensive. Assuming no complications at baseline the ICER was £19,854; with complications it increased slightly to £19,995. Similar results were obtained in the analysis based on a female cohort: estimated ICERs were less than £18,410.

The QALY differences between exenatide and glargine were small and very sensitive to the inclusion of estimates of the direct quality of life impact from weight changes. When the direct quality of life benefits arising from initial weight differences were excluded, the ICERs increased markedly in the analysis of men (incremental cost per QALY estimates were greater than £263,000). When a female population was modelled under these circumstances, exenatide had no net health advantage over insulin glargine, and was associated with higher costs.

In the UKPDS model patient weight cannot be specified to change, so in effect it remains determined by the value set at baseline. In another sensitivity analysis weight was set to be equal for both interventions at baseline, but the impact of weight changes on health-related quality of life was retained. The cost-effectiveness of exenatide worsens from the baseline estimates: in men with a starting BMI of 30 kg/m2 the analysis indicated that exenatide was still marginally more effective than glargine, but the ICERs ranged from £28,226 to £28,509.

In a sensitivity analysis in which starting BMI was increased to 35 kg/m2, the cost-effectiveness of exenatide improved markedly, with ICERs of around £1600 in men and £7000 in women.

In the scenario in which the change of HbA1c over time was slightly in exenatide's favour, the analysis indicated that exenatide was highly cost-effective, even when the direct quality of life impact from weight changes were excluded. Under these circumstances the ICERs worsen, but were between £11,130 and £12,300 for a male population with a starting BMI of 30 kg/m2.

When the starting BMI was raised to 35 kg/m2, exenatide was found to be both more effective and less costly than glargine in men. In women, the analysis indicated an ICER of only around £1000 per QALY from adopting exenatide before insulin glargine compared with moving straight to insulin glargine.

**Sitagliptin versus rosiglitazone**

For this analysis the assessment group compared rosiglitazone plus metformin and a sulfonylurea with sitagliptin plus metformin. The acquisition cost of the combined rosiglitazone/metformin formulation was used in the analysis.

The Assessment Group noted that the comparison of sitagliptin and rosiglitazone, and also the comparison of vildagliptin and pioglitazone, did not take into account side effects

associated with the use of the thiazolidinediones. The Assessment Group did not consider the use of sitagliptin or vildagliptin as dual therapy in combination with a thiazolidinedione.

Since the analysis was undertaken, the costs of the thiazolidinediones have fallen, particularly that of rosiglitazone.

It was found that the sitagliptin intervention was the dominant option (that is more effective and less costly than rosiglitazone) in the base case for both men and women, with or without considering complications at baseline. However, the difference in lifetime QALYs between the two options was small: in the case of men with a starting BMI of 30 kg/m2 this difference was estimated to be between 0.005 and 0.017as estimated by the UKPDS model in the absence of utility advantages linked with differences in weight gain associated with each option. Including these quality of life effects increases these differences to around 0.02 to 0.03 QALYs. The difference in lifetime costs between the two options ranged from around £150 to £200 per patient for both men and women.

Sitagliptin was still the dominant option in men and women if the starting BMI was raised to 35 kg/m2.

**Vildagliptin versus pioglitazone**

For this analysis the Assessment Group compared pioglitazone plus metformin and a sulfonylurea with vildagliptin plus metformin. It was assumed that pioglitazone and metformin would be provided as separate medications (that is, the combined formulation would not be used). This was because it was assumed that the dose of pioglitazone would be 30 mg/day and the dose of metformin 2 g/day. Using the combined formulation would have meant that the metformin dose would have fallen short of what was needed.

The Assessment Group attempted to consider the costs of liver function tests associated with the use of vildagliptin, assuming it to be £80 per year.

In the base-case men-only analysis, vildagliptin was slightly less effective than pioglitazone: the expected QALY difference was 0.011 with no complications at baseline and 0.007 with complications. However, the expected costs were lower with vildagliptin than pioglitazone. As a result, the ICER for pioglitazone relative to vildagliptin was £39,846 per QALY when no complications were considered and £66,799 per QALY with the complications modelled in.

For a female population, vildagliptin was found to be both a little more effective (net lifetime QALY gain ranged from 0.017 to 0.019) and less costly (net lifetime savings per patient ranged from £531 to £543) compared with pioglitazone. The Assessment Group argued that this difference between the sexes may be due to the average greater longevity of women.

Similar results were obtained by modelling a population at a starting BMI of 35 kg/m2, although in the men-only analysis there was a very slight QALY advantage over pioglitazone of only 0.004 QALYs resulting in it being the dominant option.

**Insulin glargine versus NPH insulin**

The base-case results of the comparison of insulin glargine against NPH insulin found insulin glargine to be more effective and more costly. In the case of a male population with a starting BMI of 30 kg/m2, the ICER was £281,349 per QALY (no complications at baseline) and £320,029 per QALY (with complications). Importantly, this analysis incorporates the anticipated health-related quality of life gain associated with the reduced fear of severe hypoglycaemic episodes, but the net QALY gain was only 0.007 in the 'no complications' analysis and 0.006 in the 'with complications' analysis. In the case of a female population with a starting BMI of 30 kg/m2, the ICERs are lower, but still outside conventional limits of cost effectiveness: £177,940 per QALY with no complications at baseline and £179,074 per QALY with complications. With a starting BMI of 35 kg/m2, the cost effectiveness of insulin

glargine relative to NPH insulin improves in men, but the ICERs remained well outside conventional limits of cost effectiveness (more than £189,000 per QALY). In women, the ICERs worsen.

The Assessment Group noted that these estimates do not take into account any differences in mortality that might arise from severe hypoglycaemia. This was partly because of an absence of data to inform the model.

#### Insulin detemir versus NPH insulin

The base-case results of the comparison of insulin detemir with NPH insulin found insulin detemir to be more effective and more costly. In a male population with a starting BMI of 30 kg/m2, the ICER was £187,726 per QALY with no complications at baseline and £417,625 per QALY with complications. The net QALY gains were 0.015 with no complications at baseline modelled, and 0.006 with complications. As in the comparison between insulin glargine and NPH insulin, the ICERs are lower if the analysis is undertaken on a female population with a starting BMI of 30 kg/m2 but still well outside conventional limits of cost-effectiveness: £102,007 per QALY with no complications at baseline and £113,988 per QALY with complications. Increasing the starting BMI to 35 kg/m2 improves the cost effectiveness of insulin detemir relative to NPH insulin in men, but the ICERs obtained were greater than £146,000. In women, the ICERs worsen slightly.

## 2.7 Interpreting the evidence to make recommendations

As with any decision about treatment, the choice to start, continue or withdraw a specific therapy should be made in discussion with the patient, based on all the potential harms and benefits. Recommendations on the use of the newer agents for lowering blood glucose should be viewed in this context.

### 2.7.1 Clinical effectiveness

#### 2.7.1.1 DPP-4 inhibitors (sitagliptin, vildagliptin)

The GDG discussed how DPP-4 inhibitors (sitagliptin, vildagliptin) should be used in the pathway of care, and how to identify those people or groups of people with the greatest potential to benefit.

Overall, the GDG agreed that DPP-4 inhibitors (sitagliptin and vildagliptin) were appropriate options for use in dual therapy. (See also the considerations concerning cost effectiveness in section 2.7.2.) Recommendations were also made on the use of the DPP-4 inhibitor sitagliptin[46] in triple therapy specifically when insulin use was considered inappropriate or was unacceptable to the person with diabetes. The GDG considered it appropriate to define a beneficial metabolic response for continuation of these agents. The choice of at least 0.5 percentage point reduction in HbA1c at 6 months, although not based in evidence, was agreed as a clinically important response from a starting level of 7.5% HbA1c or less; however, the GDG acknowledged that many patients will start a DPP-4 inhibitor at higher levels of HbA1c. Prescribers should be aware, as with all biochemical results, that measurement variability exists, and any test results should be interpreted in this light. There is also a need to ensure, in the absence of long-term safety data, that people do not remain on medications that do not produce the anticipated benefits. This would also ensure that HbA1c levels do not remain inadequately controlled for long periods.

46 At the time of publication, sitagliptin was the only DDP-4 inhibitor with UK marketing authorisation for use in this combination.

**HbA1c**

The GDG concluded that DPP-4 inhibitors were effective at lowering HbA1c. However, there were few relevant trials and these were generally short term (maximum follow-up of 52 weeks).

**Hypoglycaemia**

The GDG concluded that DPP-4 inhibitors were not associated with higher rates of hypoglycaemia than other newer agents. Higher rates of hypoglycaemia were seen only when a DPP-4 inhibitor was used with a sulfonylurea. Moreover, the number of hypoglycaemic episodes was fewer when a DDP-4 inhibitor rather than a sulfonylurea was added to metformin. Because of this, recommendations were made on the use of a DPP-4 inhibitor in specific groups of people with diabetes for whom hypoglycaemia was known to be a significant problem. However the GDG acknowledged the lack of direct evidence in some groups, such as older people.

**Weight**

The trials showed that, overall, DPP-4 inhibitors were not associated with either a significant loss or gain in weight. However, small differences were seen and although these may be of doubtful clinical significance (a maximum increase in weight of 0.4 kg), they become important when compared with the significant weight gain seen with other drugs such as sulfonylureas, thiazolidinediones, or insulin. The GDG therefore recommended that the decision to initiate a DPP-4 inhibitor as dual or triple therapy (sitagliptin only) should take into account the need to avoid any significant weight gain.

**Adverse effects**

Again, the GDG noted the lack of long-term safety data.

One adverse effect that may be indicated by the trial data is an association with an increased rate of infections. Prescribers should be aware of any emerging data on this and any other emerging risks, documented in post-marketing surveillance reports and the latest summary of product characteristics, and monitor as appropriate.

**Patient perspective**

No substantive evidence on patient preference or quality of life was reported in the included trials.

### 2.7.3.12 Thiazolidinediones (pioglitazone, rosiglitazone)

It should be noted that the focus of this guideline for the thiazolidinediones was the emerging safety data; the GDG therefore did not review again the data on clinical effectiveness considered for NICE clinical guideline 66. However, the GDG agreed that rosiglitazone and pioglitazone effectively reduce HbA1c and provide additional benefits in terms of glycaemic control when added to existing therapies.

The GDG discussed how thiazolidinediones should be used in the pathway of care, and how to identify those people or groups of people with the greatest potential to benefit.

Overall, the GDG agreed that thiazolidinediones (pioglitazone and rosiglitazone) were appropriate options for use in dual therapy. Recommendations were also made on the use of pioglitazone with insulin and the thiazolidinediones in triple therapy, specifically if insulin use was considered inappropriate or was unacceptable to the person with diabetes. As for the DPP-4 inhibitors, the GDG considered it appropriate to define a beneficial metabolic response for continuation of these agents. The same rationale applies for the definition of the

metabolic response (that is, at least a 0.5 percentage point reduction in HbA1c at 6 months with a starting level of 6.5% or 7.5% – a higher intervention level may be agreed with the individual). The GDG acknowledged that there were more data on safety for the thiazolidinediones (pioglitazone and rosiglitazone) than for the DPP-4 inhibitors (sitagliptin and vildagliptin), with evidence showing risks associated with both pioglitazone and rosiglitazone. The continuation criterion aims to ensure that people do not remain for long periods on medication that is ineffective at controlling their HbA1c levels.

**Adverse effects**

In the short term, the risks associated with rosiglitazone and pioglitazone include weight gain, fluid retention, peripheral oedema, expansion of plasma volume (contributing to a risk of anaemia and heart failure) and effects on lipid profiles.

Longer-term risks associated with rosiglitazone and pioglitazone include an increased risk of bone fractures in women. For rosiglitazone, there is a potentially increased risk of myocardial ischaemia based on meta-analysis of interventional trials (Diamond et al. 2007; Lago et al. 2007; Nissen and Wolski 2007; Psaty and Furberg 2007; Singh et al. 2007); pharmacoepidemiological studies show conflicting results. The risk of myocardial ischaemia and heart failure increase with concomitant insulin usage; rosiglitazone is not licensed for use with insulin. The available studies for pioglitazone, including published meta-analyses of trials (Jagger et al. 2003; Lincoff et al. 2007) and the completed long-term PROactive study (Dormandy et al. 2005), do not raise similar concerns about an increased risk of myocardial infarction in association with pioglitazone treatment. Observational studies differ with respect to their conclusions regarding the associations between thiazolidinedione use and myocardial infarction or coronary revascularisation.

Although there are few head-to-head trials of rosiglitazone and pioglitazone, it appears that, given the current evidence, rosiglitazone offers no clear benefit over pioglitazone. Moreover, pioglitazone is licensed for use with insulin.

**Patient perspective**

As noted above, safety was the focus of this guideline for the thiazolidinediones. If there is any doubt about the safety of any healthcare intervention, this should be discussed fully with the patient. The discussion should include all potential benefits and harms to allow an informed decision. Healthcare professionals should be fully aware of the latest data and guidance from the relevant safety agency (in this case, the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency). It should be noted that the agreed recommendations are fully consistent with the regulatory position as of March 2009.

### 2.7.153 GLP-1 mimetic (exenatide)

The GDG discussed how a GLP-1 mimetic (exenatide) should be used in the pathway of care, and how to identify those people or groups of people with the greatest potential to benefit.

Overall, the GDG agreed that a GLP-1 mimetic (exenatide) was not an appropriate option for use in second-line therapy. (See also considerations concerning cost effectiveness in section 2.7.2.) However, recommendations were made on the use of exenatide in third-line therapy, specifically if weight loss was an important clinical factor.

**HbA1c**

Exenatide, either alone or in combination with other oral glucose-lowering agents, was shown to be effective in lowering HbA1c. However, the GDG expressed concerns about the generalisability of some of the included trials. Key concerns were:

- the use of a comparator at a less than optimal level, for example, if insulin was not titrated to the optimal dose
- the use of comparators (insulin glargine and pre-mixed insulin with insulin aspart) that were not considered to be standard clinical practice (standard practice is NPH insulin)
- some trials did not reflect actual clinical practice; for example trials did not evaluate the effect of switching from insulin to exenatide.

Based on the limited effect of exenatide on HbA1c, but with the acceptance that any reduction was beneficial, the GDG recommended its use as an option in certain circumstances for groups of people who were considered to have the greatest potential to benefit (for example, people with a BMI ≥ 35 kg/m2 or people for whom insulin would have significant occupational implications).

**Hypoglycaemia**

The rates of hypoglycaemia were difficult to interpret because different definitions were used across the studies. However, the GDG concluded that exenatide, used in conjunction with metformin and a sulfonylurea, was not associated with higher rates of hypoglycaemia than insulin therapy.

**Weight**

The primary action of exenatide is blood glucose control, not weight loss, but the drug is associated with significant weight loss. Therefore, the GDG considered that exenatide would be a useful option in people who were obese. However, exenatide is not cost-effective unless accompanied by weight loss because it is in general more expensive but not more effective than alternative therapies. The GDG therefore recommended that a weight loss of 3% of initial body weight at 6 months (based on both the health economic modelling [see below] and an assumption that this would result in a clinically significant weight loss of 5% of initial body weight at 12 months) and adequate glucose control (minimum reduction in HbA1c of 1 percentage point over 6 months) needed to be achieved to continue its use. The GDG acknowledged that greater degrees of HbA1c improvement in the absence of weight loss might be cost effective, but no economic modelling existed to support this possibility. Lastly, if weight loss occurs without any improvement in blood glucose control, then exenatide would not be judged an appropriate and effective intervention for type 2 diabetes.

**Adverse effects**

The GDG concluded that there were limited long-term safety data on the use of exenatide. As with all drugs, particularly those that are relatively new, recommendations were based on the assumption that prescribers would be aware of any emerging risks, and would monitor as appropriate.

It should be noted that during the development of this guideline concerns were raised over the possibility of an increased risk of necrotising pancreatitis with the use of exenatide. This is a rare condition, and no trial reported any cases during follow-up (although the GDG considered that the trials generally had limited follow-up). The GDG was also aware of the latest safety guidance from national safety agencies such as the European Medicines Agency, the Medicines and Healthcare products Regulatory Agency, and the US Food and Drug Administration.

**Patient perspective**

The GDG noted the limited evidence on patient satisfaction and quality of life. The balance between the benefits for a person's weight versus the need to inject exenatide was discussed.

### 2.7.114 Long-acting insulin analogues

The GDG discussed how long-acting insulin analogues should be used in the pathway of care, and how to identify those people or groups of people with the greatest potential to benefit.

In NICE clinical guideline 66, NPH insulin was recommended as the 'preferable' choice of the initial insulin; however, based on the new cost effectiveness modelling, the GDG considered that this recommendation should be clarified, and should recommend that NPH insulin should be used as the initial insulin. (See also considerations concerning cost effectiveness in section 2.7.2.) The GDG also considered that there were situations in which the use of insulin glargine or insulin detemir could be recommended only after a trial of NPH insulin; recommendations were made on their use in subgroups with the greatest potential to benefit, based on clinical judgement.

#### HbA1c

The GDG concluded that long-acting insulin analogues were effective at lowering HbA1c.

#### Hypoglycaemia

The GDG concluded that long-acting insulin analogues were associated with lower rates of hypoglycaemia than NPH insulin, although hypoglycaemia can occur with any insulin. The GDG noted that patient education on the appropriate use of insulins was important, as was the specific insulin used. Recommendations were made on the use of long-acting insulin analogues in people for whom hypoglycaemia is particularly problematic.

#### Weight

The trials showed that the weight change with insulin glargine was similar to that associated with NPH insulin. Insulin detemir was associated with a smaller weight gain than NPH insulin, although this association disappeared when insulin detemir was used twice rather than once daily. Also, although a head-to-head trial (Rosenstock et al. 2008) showed a statistically significant smaller weight gain with insulin detemir compared with insulin glargine, the GDG considered the difference to be of doubtful clinical importance. The GDG therefore agreed that there was no convincing evidence for recommending one long-acting insulin analogue in preference to the other.

#### Adverse effects

Again, the GDG noted the lack of long-term safety data and made recommendations on the specific use of these drugs for blood glucose control.

One safety issue indicated by trial data was the increased rate of injection-site reactions with the use of insulin detemir. This may assume increased importance if it is used twice a day. Healthcare professionals should be aware of any emerging data on this and any other emerging risks, as documented in post-marketing surveillance reports and the latest summary of product characteristics, and should monitor and change treatment as appropriate.

#### Patient perspective

No substantive evidence on patient preference or quality of life was reported in the included trials. However, the GDG considered that the long-acting insulin analogues may have a role for people in whom twice-daily insulin administration is problematic – for example, people who need a healthcare professional to administer the injections.

### 2.7.12 Cost effectiveness

The GDG recognised the many strengths but also the limitations of using the UK Prospective Diabetes Study (UKPDS) Outcomes Model as a basis for modelling because it predicts only the first event in any single category of diabetes-related complications. In addition, not all relevant complications are included in the model (for example, peripheral neuropathy is excluded). Moreover, there was concern that the UKPDS may fail to adequately capture the impact of weight changes on health-related quality of life, or diabetic complications that occur infrequently. The GDG acknowledged that measures of adiposity may not independently increase the risk of some diabetic complications. Given these limitations, the analysis developed by the Assessment Group attempted to take into account potential direct quality of life gains associated with weight changes and the reduced fear of hypoglycaemic episodes. The Assessment Group also attempted to explore the impact of changing the baseline rate of complications.

The GDG recognised that the current available direct evidence did not include all the comparisons of interest. One approach to inform decision-making under these circumstances is to undertake an indirect treatments analysis. The GDG understood that when undertaking an indirect or mixed-treatment comparison (the latter refers to an analysis that combines both indirect and direct evidence) the principles of good practice for standard meta-analyses should be followed. In addition, it is critical that trial randomisation is preserved.

As part of the Assessment Group's initial modelling, a simple indirect treatments analysis was undertaken. However, the GDG was concerned that the degree of heterogeneity across the relevant studies would make such analysis difficult to undertake and interpret. The Assessment Group was also concerned about the validity of these analyses. As a result, the GDG focused its attention on the pair-wise analyses presented by the Assessment Group, taking account of published health economic evidence.

The GDG noted that the Assessment Group provided cost-effectiveness estimates separately for men and women. Although it understood the reasons for doing that, the GDG considered that there was no clear evidence to develop recommendations according to sex.

The GDG noted that cost-effectiveness estimates provided by the Assessment Group can be particularly sensitive to the inclusion of direct quality of life gains associated with body weight changes or the reduced fear of hypoglycaemic episodes. In addition, the GDG noted that the estimated differences between alternative regimens in terms of both costs and benefits could be slight, particularly with regard to benefits. The GDG's view was therefore that it was difficult to distinguish between some of the alternative options.

#### 2.7.251 Thiazolidinediones (pioglitazone, rosiglitazone) and the DPP-4 inhibitors (sitagliptin, vildagliptin)

The GDG was aware that the thiazolidinediones (pioglitazone and rosiglitazone) were not compared with each other in the present cost-effectiveness analysis; nor were they compared with the combination of metformin and sulfonylurea in a situation in which a thiazolidinedione can replace either metformin or a sulfonylurea and be used as second-line therapy. The Assessment Group assessed the cost effectiveness of these agents only against sitagliptin and vildagliptin as third-line interventions. The Assessment Group's focus was on the latest safety information on these agents. Consequently the GDG not only took into account the economic analysis developed by the Assessment Group to inform the present guideline but also considered the economic review undertaken for NICE clinical guideline 66, which also considered the use of the thiazolidinediones as third-line interventions. On this basis it was the GDG's view that the thiazolidinediones were options for use in dual therapy. The GDG also considered that these agents were suitable for use in triple therapy specifically when insulin use was considered inappropriate or was unacceptable to the person with diabetes.

The GDG recognised that the de novo modelling for the present guideline did not take into account the potentially significant adverse events that may be associated with use of the thiazolidinediones. However, the GDG noted that there was an absence of long-term data on the safety of the DPP-4 inhibitors. The de novo model appeared to indicate that the DPP-4 inhibitors were more cost effective than the thiazolidinediones. However, as noted above, differences in benefits appeared to be small. In terms of cost, the GDG was particularly aware that the acquisition costs of the thiazolidinediones were lower than that modelled by the Assessment Group and are likely to fall further in the next few years when these agents come off patent. The GDG was therefore persuaded that it was not possible to usefully distinguish between thiazolidinediones and the DPP-4 inhibitors in terms of cost effectiveness.

The GDG considered that the DPP-4 inhibitors were cost-effective options for use in dual therapy (that is in combination with either metformin or a sulfonylurea). There was no evidence on clinical and cost-effectiveness grounds that would suggest there are any significant differences between the DPP-4 inhibitors. The GDG considered that these drugs were likely to be highly cost-effective alternatives to relevant comparators. The GDG also believed that sitagliptin is a suitable option in triple-therapy regimens specifically if insulin use is considered inappropriate or is unacceptable to the person with diabetes.

#### 2.7.292 GLP-1 mimetic (exenatide)

Relative to insulin glargine, the de novo economic analysis appeared to indicate that exenatide was potentially a highly cost-effective option at a starting BMI of 30 kg/m2. However, the GDG noted that these results could be particularly sensitive to certain important assumptions, for example in relation to its impact on patient weight. Indeed, exenatide was estimated to be highly cost-ineffective relative to insulin glargine when the direct health-related quality of life impact of weight changes were excluded from the analysis, under the scenario in which HbA1c increase was slower with insulin glargine than with exenatide. The GDG also noted the results of the pair-wise comparison between insulin glargine and NPH insulin, which appeared to indicate that insulin glargine was highly cost ineffective compared with NPH insulin. NPH insulin represents a more suitable comparator for exenatide. The comparison of exenatide and NPH insulin would have needed indirect modelling, and was not performed.

Given these data, the GDG was not persuaded that exenatide should routinely be used at a starting BMI of less than 35 kg/m2. The GDG nevertheless considered that there could be situations in which the benefits obtained would result in exenatide being a cost-effective choice. The GDG therefore recommended that exenatide be considered an option only for people considered to have the greatest potential to benefit, particularly with regard to weight loss. Therefore the GDG considered that a person should have a starting BMI of 35 kg/m2 before being considered for treatment with exenatide. If the starting BMI is less than 35.0 kg/m2, the GDG believed that exenatide therapy should be considered only for those in whom therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. The GDG considered it important to consider stopping rules that incorporated both a decrease in HbA1c and decrease in body weight. It was therefore the GDG's view that exenatide therapy should be continued only if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

#### 2.7.273 Long-acting insulin analogues (insulin glargine and insulin detemir)

The long-acting insulin analogues (glargine and detemir) did not appear to be cost-effective options when compared with NPH insulin in the analysis undertaken by the Assessment Group. However, the GDG accepted that episodes of hypoglycaemia have the potential to be highly detrimental to a person's health-related quality of life. This is partly because of a

person's fear of symptomatic hypoglycaemic episodes. The Assessment Group attempted to take this aspect into consideration in the modelling. In addition, a person's health-related quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control.

Taking these considerations into account, it was the GDG's view that when starting basal insulin therapy NPH insulin should be preferred on the basis of its cost effectiveness and well-known safety profile. The GDG concluded that it would be more cost effective to target the use of the long-acting insulin analogues to those people with type 2 diabetes who would be most likely to benefit, particularly people whose lifestyle is significantly restricted by symptomatic hypoglycaemic episodes. The GDG considered that there was no convincing evidence to recommend one long-acting insulin analogue in preference to another under these circumstances. In addition, the GDG accepted that, on the balance of probabilities, the healthcare resources spent on helping people who need assistance with their insulin injections would be reduced significantly (mainly in terms of the time spent by healthcare professionals in giving the injections) to the extent that the use of insulin analogues in this group is likely to be cost effective.

## 2.8 Research recommendations

- What are the clinical and cost effectiveness and safety of GLP-1 mimetics for the long-term management of blood glucose control in people with type 2 diabetes? Are there specific subgroups in which these agents are more clinically and/or cost effective?
  - There is a lack of long-term evidence (12 months or longer) on the clinical and cost effectiveness of GLP-1 mimetics compared with standard UK practice (including lifestyle interventions) or with other newer agents. Studies should report clinically relevant outcomes and patient-centred outcomes.
- Which subgroup(s) of people with type 2 diabetes, if any, would benefit from replacing insulin with GLP-1 mimetics?
  - There is limited evidence on the effect of replacing insulin with a GLP-1 mimetic, and it is not clear whether there are specific subgroups of people with type 2 diabetes who would benefit more than the general population from such an intervention.
- What are the clinical and cost effectiveness and safety of DPP-4 inhibitors for the long-term management of blood glucose control in people with type 2 diabetes? And are there specific subgroups in which these agents are more clinically and/or cost effective?
  - There is a lack of long-term evidence (12 months or longer) on the effectiveness and cost-effectiveness of DPP-4 inhibitors compared with standard UK practice (including lifestyle interventions) or against other newer agents. Studies should report clinically relevant outcomes and patient-centred outcomes.
- What are the clinical and cost effectiveness of insulin and a GLP-1 mimetic (exenatide) used in combination for the management of blood glucose control in people with type 2 diabetes?
  - This combination does not currently have UK marketing authorisation but does appear logical and appropriate. There is also some anecdotal evidence that this combination is being used in current practice. Evidence on its effectiveness and safety is therefore needed.
- How do rates of adherence differ with different complexities of treatment regimen for the management of type 2 diabetes? Do these differ over time or according to the route of administration?
  - Evidence is needed on whether the complexities of the treatments for type 2 diabetes affect adherence or, more importantly, clinical outcomes (such as blood glucose control) and patient outcomes (such as health-related quality of life).

- How does the initiation and titration of long-acting insulin for the management of blood glucose control in people with type 2 diabetes affect health-related quality of life? What are the health-related quality of life changes associated with the experience of, or the fear of hypoglycaemia?
  - Ideally, changes in health-related quality of life should be assessed using a standardised and validated generic instrument, preferably the EQ–5D.
- What is the direct effect on health-related quality of life associated with weight loss, or of avoiding weight gain, for people with type 2 diabetes?

# 3 References, glossary and abbreviations

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# 3.2 Glossary and abbreviations

## 3.2.1 Glossary

**Cohort study**

(also known as follow-up, incidence, longitudinal, or prospective study): an observational study in which a defined group of people (the cohort) is followed over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

**Comorbidity**

Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

**Confidence interval (CI)**

The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)

**Cost-effectiveness analysis (CEA)**

An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio (ICER).

**Economic evaluation**

Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision-making framework.

**Guideline Development Group (GDG)**

A group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines Technical Team who develop the recommendations for a clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

**Generalisability**

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

**Heterogeneity**

A term used to illustrate the variability or differences between studies in the estimates of effects.

**Odds ratio (OR)**

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

**Quality-adjusted life year (QALY)**

A statistical measure, representing 1 year of life with full quality of life.

**Randomised controlled trial**

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

**Relative risk (RR)**

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

**Systematic review**

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

## 3.22 Abbreviations

| | |
|---|---|
| BMI | body mass index |
| CI | confidence interval |
| DPP-4 | dipeptidyl peptidase-4 |
| GLP-1 | glucagon-like peptide-1 |
| HbA1c | glycated haemoglobin |
| HDL | high-density lipoprotein |
| ICER | incremental cost-effectiveness ratio |
| OR | odds ratio |
| QALY | quality-adjusted life year |
| RR | relative risk |
| SPC | summary of product characteristics |
| UKPDS | UK Prospective Diabetes Study |

# 4 Methods

## 4.1 Aim and scope of the guideline

### 4.1.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 6.1). The scope of this guideline is available in appendix 6.1 and from www.nice.org.uk/guidance/index.jsp?action=download&o=40178

The aim of this guideline is to provide evidence-based recommendations to guide healthcare professionals in the use of newer agents in the treatment of adults with type 2 diabetes. Pregnant women with diabetes were not included in the scope of this guideline.

## 4.2 Development methods

This section sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the previous chapters of this guideline. The methods used to develop the recommendations are in accordance with those set out by the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') in 'The guidelines manual 2007' (available at: www.nice.org.uk).

### 4.2.1 Developing the guideline scope

The draft scope, which defined the areas the guideline would and would not cover, was prepared by the Short Clinical Guidelines Technical Team on the basis of the remit from the Department of Health, consultation with relevant experts and a preliminary search of the literature to identify existing clinical practice guidelines, key systematic reviews and other relevant publications. The literature search gave an overview of the issues likely to be covered by the guideline and helped define key areas. It also informed the Short Clinical Guidelines Technical Team of the volume of literature likely to be available in the topic area, and therefore the amount of work required.

The draft scope was tightly focused and covered one clinical topic area, namely the use of newer agents in the treatment of adults with type 2 diabetes.

The draft scope was the subject of public consultation.

### 4.2.2 Forming and running the Short Clinical Guideline Development Group (GDG)

The short clinical guideline on type 2 diabetes: newer agents was developed by a GDG consisting of 12 members, two co-opted experts, one of whom attended one session of a GDG meeting, and the Short Clinical Guidelines Technical Team. The GDG had a Chair, healthcare professional members and patient/carer members, who were recruited through open advertisement. Development took 7 months and the GDG met on four occasions, every 8 weeks.

### 4.2.3 Commissioning the technology assessment report

For this guideline, a technology assessment report was commissioned by the UK Health Technology Assessment (HTA) Programme from the Aberdeen Health Technology Assessment Group. This technology assessment report was used as the primary source of evidence considered by the GDG.

The Aberdeen HTA Group is based in the Institute of Applied Health Sciences (IAHS), College of Medicine and Life Sciences, University of Aberdeen. The Institute is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, the Public Health Research Unit and the Health Economics Research Unit.

The HTA Group carries out independent health technology assessment reports for the UK HTA Programme, which commissions these for NICE and other bodies such as the National Screening Committee. The group has produced previous technology assessment reports on diabetes, including:

- continuous subcutaneous insulin infusions (insulin pumps)
- screening for type 2 diabetes
- prevention of diabetes by non-pharmacological interventions in people with impaired glucose regulation
- inhaled insulin.

The Aberdeen HTA Group also writes Cochrane reviews on diabetes.

### 4.2.4 Developing the review protocol

The third step in the development of the guidance was to refine the scope into a review protocol for the technology assessment report. The protocol formed the starting point for the subsequent evidence reviews and facilitated the development of recommendations by the GDG.

The protocol was developed by the Aberdeen HTA Group with assistance from the Short Clinical Guidelines Technical Team and the GDG Chair. The final protocol is shown in appendix 6.2.

The GDG and Short Clinical Guidelines Technical Team reviewed the proposed review parameters (inclusion and exclusion criteria) and comparators for each topic area, and suggested revisions as appropriate. The Aberdeen HTA Group then made revisions to the draft technology assessment report to address any agreed changes. The final technology assessment report is shown in appendix 6.2

### 4.2.5 Literature search

The search strategies for the evidence review were developed by the Aberdeen HTA Group. The strategies were run across a number of databases, with no date restrictions imposed on the searches.

Because the technology assessment report included de novo health economic modelling, no further searches were undertaken to identify other published health economic evaluations.

In addition to the systematic literature searches, the GDG was asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

### 4.2.6 Reviewing the evidence

The Aberdeen HTA Group had primary responsibility for reviewing the evidence but was supported by the Short Clinical Guidelines Technical Team as appropriate. The methods of the technology assessment report are shown in appendix 6.2.

Studies suggested or submitted by the GDG and expert advisers were also reviewed for relevance to the key clinical questions and included if they met the inclusion criteria.

The Short Clinical Guidelines Technical Team was responsible for ensuring that appropriate review methods were used and that the final review met the needs of the GDG.

## 4.237 Grading the evidence

### Intervention studies

Studies that meet the minimum quality criteria were ascribed a level of evidence to help the guideline developers and the eventual users of the guideline understand the type of evidence on which the recommendations have been based.

There are many different methods for assigning levels to the evidence and there has been considerable debate about which system is best. A number of initiatives are currently underway to find an international consensus on the subject. NICE has previously published guidelines using different systems and is now examining a number of systems in collaboration with the National Collaborating Centres and academic groups throughout the world to identify the most appropriate system for future use.

Until a decision is reached on the most appropriate system for NICE guidelines, the Short Clinical Guidelines Technical Team will use the system for evidence shown in table 1.

**Table 1 Levels of evidence for intervention studies**

Reproduced with permission from the Scottish Intercollegiate Guidelines Network.

| Level of evidence | Type of evidence |
|---|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias[a] |
| 1– | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of biasa |
| 2++ | High-quality systematic reviews of case–control or cohort studies<br>High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |
| 2– | Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causala |
| 3 | Non-analytic studies (for example, case reports, case series) |
| 4 | Expert opinion, formal consensus |

[a] Studies with a level of evidence '–' should not be used as a basis for making a recommendation
RCT, randomised controlled trial.

## 4.238 Interpreting the evidence to make recommendations

The evidence review for the key clinical questions being discussed was made available to the GDG 1 week before the scheduled GDG meeting.

All GDG members were expected to have read the evidence review before attending each meeting. The review of the evidence had three components. First, the GDG discussed the evidence report and corrected any factual errors or incorrect interpretation of the evidence. Second, evidence statements, which had been drafted by the Short Clinical Guidelines Technical Team, were presented to the GDG and the GDG agreed the correct wording of

these. Third, from a discussion of the evidence statements and the experience of GDG members, recommendations were drafted. The Short Clinical Guidelines Technical Team explicitly flagged up with the GDG that it should consider the following criteria (considered judgement) when developing the guideline recommendations from the evidence presented:

- internal validity
- consistency
- generalisability (external validity)
- clinical impact
- cost effectiveness
- ease of implementation
- patients' perspective
- overall synthesis of evidence.

For each key question, recommendations were derived from the evidence summaries and statements presented to the GDG. The recommendations were evidence based if possible; if evidence was not available, informal consensus of opinion within the GDG was used. The need for future research was also specified. The process by which the evidence statements informed the recommendations is summarised in the section 'Interpreting the evidence to make recommendations' in the relevant evidence review.

### 4.2.9 Health economics

An economic evaluation aims to integrate data on the benefits (ideally in terms of QALYs), harms and costs of alternative options. An economic appraisal will consider not only whether a particular course of action is clinically effective, but also whether it is cost effective (that is, value for money). If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to redirect resources to other activities that yield greater health gain.

A systematic review of the economic literature relating to the use of newer agents in type 2 diabetes was also conducted. In addition, the GDG and expert advisers were questioned over any potentially relevant unpublished data.

Health economics statements are made in the guideline in sections in which the use of NHS resources is considered.

### 4.2.10 Consultation

The draft of this guideline was available on the NICE website for consultation, and registered stakeholders were informed by NICE that the documents were available. Non-registered stakeholders could view the guideline on the website.

### 4.2.11 Other related NICE guidance

NICE has issued the following related guidance:

- Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 87. Available from www.nice.org.uk/CG87

### 4.2.12 Piloting and implementation

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. These limitations excepted, every effort has been made to maximise the relevance of recommendations to the intended audience through the use of a GDG with relevant professional and patient involvement, by use of relevant experienced

expert reviewers and the stakeholder process facilitated by the NICE Short Clinical Guidelines Technical Team. Implementation support tools for this guideline will be available from the Implementation Team at NICE.

### 4.2.13 Audit methods

The guideline recommendations have been used to develop clinical audit support for monitoring local practice. This is an essential implementation tool for monitoring the uptake and impact of guidelines, and thus needs to be clear and straightforward for organisations and professionals to use.

NICE develops audit support for all its guidance programmes as part of its implementation strategy.

### 4.2.14 Scheduled review of this guideline

The guidance has been developed in accordance with the NICE guideline development process for short clinical guidelines. This has included allowing registered stakeholders the opportunity to comment on the draft guidance. In addition, the first draft was reviewed by an independent Guideline Review Panel established by NICE.

The comments made by stakeholders, peer reviewers and the Guideline Review Panel were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG, and the Short Clinical Guidelines Technical Team recorded the agreed responses.

This guideline will be considered for an update after 3 years, according to the Update process described in 'The guidelines manual' (available at www.nice.org.uk).

# 5 Contributors

## 5.1 The Guideline Development Group (GDG)

The GDG was composed of relevant healthcare professionals, patient/carer representatives and NICE technical staff.

The members of the GDG are listed below.

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The following people were not full members of the GDG but were co-opted onto the group as expert advisers:

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**Andrew Krentz**

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The following individual contributed expertise:

**Alistair Gray**

Director of the Health Economics Research Centre, Division of Public Health and Primary Care, University of Oxford

## 5.15.1 The Short Clinical Guidelines Technical Team

The Short Clinical Guidelines Technical Team was responsible for this guideline throughout its development. It was responsible for preparing information for the GDG, for drafting the guideline and for responding to consultation comments. The following people, who are employees of NICE, made up the technical team working on this guideline.

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## 5.11 Guideline Review Panel

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**John Harley**

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**Ailsa Donnelly**

Lay member

## 5.12 List of stakeholders

Advisory Committee for Community Dentistry

Association for Clinical Biochemistry

Association of British Clinical Diabetologists (ABCD)

AstraZeneca UK Ltd

Barnsley Hospital NHS Foundation Trust

Barnsley Primary Care Trust

Boehringer Ingelheim Ltd

Bournemouth and Poole Primary Care Trust

Bristol-Myers Squibb Pharmaceuticals Ltd

British Geriatrics Society

British Heart Foundation

British National Formulary (BNF)

British Renal Association, The

British Society for Human Genetics

Buckinghamshire Primary Care Trust

BUPA

Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's)

Cardiff Research Consortium

Care Quality Commission (CQC)

Commission for Social Care Inspection

Connecting for Health

Conwy Local Health Board

Cornwall and Isles of Scilly Primary Care Trust

1 Countess of Chester Hospital NHS Foundation Trust
2 Coventry and Warwickshire Cardiac Network
3 Daiichi Sankyo UK
4 Department for Communities and Local Government
5 Department of Health
6 Department of Health, Social Security and Public Safety of Northern Ireland
7 Derbyshire County Primary Care Trust
8 Devon Primary Care Trust
9 DHSSPSNI
10 Diabetes UK
11 Education for Health
12 Faculty of Dental Surgery
13 Faculty of Public Health
14 GlaxoSmithKline UK
15 Guy's and St Thomas' NHS Trust
16 Halton and St Helens Primary Care Trust
17 Hertfordshire Partnership NHS Trust
18 Heywood Middleton and Rochdale Primary Care Trust
19 Hyperlipidaemia Education and Atherosclerosis Research Trust (HEART UK)
20 Institute of Biomedical Science
21 Insulin Dependent Diabetes Trust
22 Janssen-Cilag Ltd
23 Johnson & Johnson Medical
24 Kingston Hospital NHS Trust
25 Leeds Primary Care Trust
26 Leeds Teaching Hospitals NHS Trust
27 Lilly UK
28 Luton and Dunstable Hospital NHS Foundation Trust
29 Maidstone Hospital
30 Maternity Health Links
31 McNeil Nutritionals
32 Medicines and Healthcare products Regulatory Agency (MHRA)
33 Merck Serono

1 Merck Sharp & Dohme Ltd
2 Milton Keynes Primary Care Trust
3 National Diabetes Consultant Nurse Group
4 National Obesity Forum
5 National Patient Safety Agency (NPSA)
6 National Prescribing Centre
7 National Public Health Service – Wales
8 National Treatment Agency for Substance Misuse
9 NCCHTA
10 NHS Clinical Knowledge Summaries Service (SCHIN)
11 NHS Kirklees
12 NHS Knowsley
13 NHS Plus
14 NHS Purchasing and Supply Agency
15 NHS Quality Improvement Scotland
16 NHS Sefton
17 NHS Sheffield
18 North Cheshire Hospitals
19 North Staffordshire Primary Care Trust
20 North Yorkshire and York Primary Care Trust
21 Northern Ireland Chest Heart Stroke
22 Northumbria Diabetes Service
23 Nottinghamshire County Teaching Primary Care Trust
24 Novartis Pharmaceuticals UK Ltd
25 OSI Pharmaceuticals
26 PERIGON Healthcare Ltd
27 Pfizer Limited
28 Plymouth Teaching Primary Care Trust
29 Primary Care Cardiovascular Society
30 Primary Care Diabetes Society
31 Roche Products Limited
32 Royal Brompton & Harefield NHS Trust
33 Royal College of General Practitioners

1 Royal College of Midwives
2 Royal College of Nursing
3 Royal College of Paediatrics and Child Health
4 Royal College of Pathologists
5 Royal College of Physicians London
6 Royal United Hospital Bath NHS Trust
7 SACAR
8 Sanofi-Aventis
9 Scarborough and North Yorkshire Healthcare NHS Trust
10 Schering-Plough Ltd
11 Scottish Intercollegiate Guidelines Network (SIGN)
12 Sedgefield Primary Care Trust
13 Servier Laboratories
14 Sheffield Primary Care Trust
15 Sheffield Teaching Hospitals NHS Foundation Trust
16 Shrewsbury and Telford Hospital NHS Trust
17 Social Care Institute for Excellence (SCIE)
18 Solihull Care Trust
19 South Asian Health Foundation
20 South London and Maudsley NHS Foundation Trust
21 South Staffordshire Health Authority
22 Swansea NHS Trust
23 Swindon and Marlborough NHS Trust
24 Takeda UK Ltd
25 Tameside Acute Trust
26 Teva UK Ltd
27 The British Dietetic Association
28 Trafford Primary Care Trust
29 UCLH NHS Foundation Trust
30 United Kingdom Clinical Pharmacy Association (UKCPA)
31 University College London
32 University of Nottingham
33 Walsall Primary Care Trust

1 Welsh Assembly Government

2 Welsh Endocrine and Diabetes Society

3 Welsh Scientific Advisory Committee (WSAC)

4 West Hertfordshire Primary Care Trust and East and North Hertfordshire Primary Care Trust

5 West Herts Hospitals NHS Trust

6 Western Cheshire Primary Care Trust

7 Western Health and Social Care Trust

8 Wirral University Teaching Hospital NHS Foundation Trust

9 York NHS Foundation Trust

# 5.2 Declarations

## 5.2.1 Authorship and citation

12 Authorship of this full guideline document is attributed to the NICE Short Clinical Guidelines
13 Technical Team and members of the GDG under group authorship.

14 The guideline should be cited as: National Institute for Health and Clinical Excellence (2009)
15 Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. Available from
16 www.nice.org.uk/CG87ShortGuideline

## 5.2.2 Declarations of interest

18 A full list of all declarations of interest made by this GDG is available on the NICE website
19 (www.nice.org.uk).

## 5.2.3 Acknowledgments

21 The Short Clinical Guidelines Technical Team thanks the Aberdeen Health Technology
22 Assessment Group for producing the Technology Assessment Report, without which the
23 production of this guideline would not have been possible.