SHORT CLINICAL GUIDELINE
SCOPE

1 Guideline title

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

1.1 Short title

Type 2 diabetes newer agents

2 Background

a) The Department of Health has asked the National Institute for Health and Clinical Excellence (‘NICE’ or ‘the Institute’) to develop a short clinical guideline on ‘newer agents for blood glucose control in type 2 diabetes’ for use in the NHS in England and Wales. This will be a rapid update of the relevant section of the NICE clinical guideline ‘Type 2 diabetes: the management of type 2 diabetes (update)’. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute’s clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care for which a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisal guidance published by NICE after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and
their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Type 2 diabetes is a chronic metabolic disorder caused by insulin insensitivity and a failure of pancreatic insulin and glucagon secretion to compensate for this. It can be associated with acute metabolic disturbances such as hyperglycaemia (high blood glucose). If prolonged, hyperglycaemia can cause microvascular and macrovascular damage. Good management of blood-glucose levels, blood pressure and lipid levels is known to delay or prevent the long-term complications of diabetes. Current practice is that treatment should aim to achieve a glycated haemoglobin (HbA1c) level of 6.5%, or 7.5% for those at risk of severe hypoglycaemia, although it is acknowledged that such targets may not be achieved in everyone.

b) The prevalence of diabetes is around 3.7% in England and 4.21% in Wales; diabetes affects more than 2.09 million people in England and Wales. More than 85% of these people have type 2 diabetes, and it is accepted that there are also many people who have undiagnosed type 2 diabetes. It has been estimated that diabetes may be responsible for at least 5% of healthcare expenditure in the UK, and up to 10% of hospital budgets are used for the care of people with diabetes. Type 2 diabetes usually occurs in people older than 40; however, it can appear earlier in life, particularly in people of South Asian or African-Caribbean origin.

c) Although lifestyle interventions (diet and exercise) are the first-line treatments for the management of type 2 diabetes, in most cases the condition is progressive and people will usually need to take oral glucose-lowering drugs. Metformin is widely-used as first-line oral therapy, with sulphonylurea as an ‘add on’ second-line therapy if glycaemic control remains poor, but clinical practice varies...
according to patient attributes (such as body weight and insulin sensitivity). Current NICE guidance (NICE technology appraisal guidance 63) is that glitazones (thiazolidinediones) are not recommended as second-line therapy for most people. Because type 2 diabetes tends to progress, as a result of the continuing failure of insulin secretion, many patients eventually need to take insulin. Insulin therapy may be given in a number of different forms, for example intermediate-acting insulin (NPH insulin) or biphasic insulin (premix) or basal bolus regimens.

d) In recent years new drugs have been developed for blood glucose control. These include the long-acting insulin analogues (insulin glargine and insulin detemir), incretin mimetics (exenatide and liraglutide) and incretin enhancers (sitagliptin and vildagliptin). So far only insulin glargine has been the subject of NICE guidance (NICE technology appraisal guidance 53). There is an urgent need for guidance that determines the role of all of these agents and their place in the care pathway of blood glucose control for people with type 2 diabetes. The place of thiazolidinediones (rosiglitazone and pioglitazone) within this pathway also needs to be addressed, including their positioning relative to the newer agents, and there are recent safety concerns specifically in relation to rosiglitazone to be addressed regarding the risk of cardiovascular adverse events.

e) The NICE clinical guideline ‘Type 2 diabetes: the management of type 2 diabetes (update)’ is scheduled for publication in May 2008. It makes recommendations on the use of thiazolidinediones (rosiglitazone and pioglitazone), an incretin mimetic (exenatide) and a long-acting insulin analogue (insulin glargine). These recommendations will be reviewed and updated by this short guideline.
4 The guideline

a) The guideline development process is described in detail in four publications that are available from the NICE website (see ‘Further information’). ‘The guideline development process: an overview for stakeholders, the public and the NHS’ describes how organisations can become involved in the development of a guideline. ‘The guidelines manual’ provides advice on the technical aspects of guideline development. ‘Background and overview of the short guidelines programme’ and ‘The short guideline process – consultation document’ describe short clinical guidelines and how they are developed.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 and older) diagnosed with type 2 diabetes.

b) Specific patient subgroups (for example, based on cardiovascular risk or ethnicity) for whom the impact of these agents might differ.

4.1.2 Groups that will not be covered

a) People with type 2 diabetes who are younger than 18 years.

b) Pregnant women with type 2 diabetes or gestational diabetes.

4.2 Healthcare setting

Primary and secondary care.
4.3 **Clinical management**

4.3.1 **Areas covered by the guideline**

a) The newer agents for the control of blood glucose in type 2 diabetes that are detailed in 4.3.1 e–n. The relevant comparators for these interventions are:

- oral glucose-lowering medications (metformin or sulphonylurea) used alone or in combination
- intermediate-acting, long-acting or biphasic (premix) insulins.

b) Comparison of the newer agents with each other, if relevant evidence is available.

c) Use of these newer agents and their positioning within the care pathway of glucose control in patients with type 2 diabetes.

d) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug’s summary of product characteristics to inform their decisions for individual patients.

**Incretin enhancers (DPP-4 inhibitors)**

e) Sitagliptin (Januvia, Merck Sharp & Dohme). Sitagliptin has UK marketing authorisation for use in patients with type 2 diabetes mellitus as oral therapy to improve glycaemic control in combination with:

- metformin if diet and exercise plus metformin do not provide adequate glycaemic control
- a sulphonylurea, in patients with insufficient glycaemic control despite the maximum tolerated dose of a sulphonylurea and for whom metformin is inappropriate because of contraindications or intolerance
• a sulphonylurea and metformin, in patients with insufficient glycaemic control
• a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

f) Vildagliptin (Galvus, Novartis). Vildagliptin has UK marketing authorisation for use in the treatment of type 2 diabetes mellitus as dual oral therapy in combination with:

• metformin, in patients with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin
• a sulphonylurea, in patients with insufficient glycaemic control despite the maximum tolerated dose of a sulphonylurea and for whom metformin is inappropriate because of contraindications or intolerance
• a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

Incretin mimetics (GLP-1 analogues)
g) Exenatide (Byetta, Eli Lilly and Company). Exenatide currently has UK marketing authorisation for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in people who have insufficient glycaemic control on the maximum tolerated doses of these oral therapies. It is administered as a subcutaneous injection.

h) Liraglutide (NN2211, Novo Nordisk). Liraglutide does not yet have UK marketing authorisation. It has been studied in phase III trials in patients with type 2 diabetes who have been treated with oral glucose-lowering medications (metformin and a sulphonylurea). These studies have examined the use of liraglutide as monotherapy and as combination with metformin, sulphonylureas, metformin and a sulphonylurea, and metformin and a thiazolidinedione. Liraglutide has also been studied in combination with a sulphonylurea, and in combination with a thiazolidinedione.
Liraglutide will be considered according to its anticipated licensed indication. Guidance on this intervention will be issued only if it achieves UK marketing authorisation for use in type 2 diabetes.

**Thiazolidinediones**

i) Pioglitazone (Actos, Takeda). Pioglitazone is administered orally and has UK marketing authorisation for use:

- as monotherapy in people (particularly those who are overweight) who have insufficient glycaemic control from diet and exercise, and for whom metformin is inappropriate because of contraindications of intolerance
- as dual oral therapy in combination with metformin in people (particularly those who are overweight) with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin
- as dual oral therapy in combination with a sulphonylurea, only in people who show intolerance to metformin or for whom metformin is contraindicated, and who have insufficient glycaemic control despite the maximum tolerated dose of monotherapy with a sulphonylurea
- as triple therapy in combination with metformin and a sulphonylurea, in people (particularly those who are overweight) with insufficient glycaemic control despite dual oral therapy
- in combination with insulin in people with type 2 diabetes with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

j) Pioglitazone/metformin combination (Competact, Takeda). This combination product is administered orally and is indicated for the treatment of type 2 diabetes, particularly in people who are overweight, and who are unable to achieve sufficient glycaemic control at the maximum tolerated dose of oral metformin alone.
k) Rosiglitazone (Avandia, GlaxoSmithKline UK). Rosiglitazone is indicated for the treatment of type 2 diabetes and has UK marketing authorisation for use:

- as oral monotherapy in people (particularly those who are overweight) who have insufficient glycaemic control from diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
- as dual oral therapy in combination with metformin in people (particularly those who are overweight) with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin
- as dual oral therapy in combination with a sulphonylurea, only in people who show intolerance to metformin or for whom metformin is contraindicated, and who have insufficient glycaemic control despite the maximum tolerated dose of monotherapy with a sulphonylurea
- as triple therapy in combination with metformin and a sulphonylurea, in people (particularly those who are overweight) with insufficient glycaemic control despite dual oral therapy.

l) Rosiglitazone/metformin combination (Avandamet, GlaxoSmithKline UK). This combination has UK marketing authorisation for oral use in people for whom the maximum tolerated dose of oral metformin alone does not provide sufficient glycaemic control. It also has UK marketing authorisation for use as triple oral therapy with a sulphonylurea in people with insufficient glycaemic control despite dual oral therapy with the maximum tolerated dose of metformin and a sulphonylurea.

**Long-acting recombinant human insulin analogues**

m) Insulin detemir (Levemir, Novo Nordisk). Insulin detemir is indicated for the treatment of diabetes mellitus, including use with oral hypoglycaemia agents. It is administered via subcutaneous injection.
n) Insulin glargine (Lantus, Sanofi Aventis). Insulin glargine is indicated for the treatment of diabetes mellitus, including use with oral hypoglycaemia agents. It is administered via subcutaneous injection.

4.3.2 **Areas not covered by the guideline**

a) Diagnosis of type 2 diabetes.

b) Treatments other than the ones listed in 4.3.1 e–n.

4.4 **Outcome measures**

a) Efficacy and tolerability of the newer agents for blood glucose control, and their impact on the control of type 2 diabetes including:

- changes in blood glucose control
- changes in HbA₁₀ levels
- frequency and severity of hypoglycaemic episodes
- changes in weight control and body mass index.

b) Impact of the newer agents for blood glucose control on the development of complications associated with type 2 diabetes:

- microvascular – retinopathy, nephropathy
- macrovascular – heart disease, stroke, peripheral vascular disease.

c) Any adverse events reported that are considered to be associated with the specified newer agents for blood glucose control.

d) Resource use.

e) Health-related quality of life.

f) Mortality.
4.5 **Economic aspects**
Costs will be considered from an NHS and Personal Social Services perspective.

4.6 **Status**

4.6.1 **Scope**
This is the final version of the scope.

4.6.2 **Related NICE guidance**
This short guideline will update the NICE standard clinical guideline 'Type 2 diabetes: the management of type 2 diabetes (update)', which will in turn update the following NICE guidance:


NICE is also developing the following related guidance:


4.6.3 **Guideline**
The development of the guideline recommendations will begin in May 2008.

5 **Further information**
Information on the guideline development process is provided in:

- ‘The guideline development process: an overview for stakeholders, the public and the NHS’
• ‘Guideline development methods: information for national collaborating centres and guideline developers’
• ‘Background and overview of the short guidelines programme’
• ‘The short guideline process – consultation document’.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesprocess). Information on the progress of the guideline will also be available from the website.