

**Guidance on
the use of
long-acting
insulin analogues
for the
treatment of
diabetes – insulin
glargine**

Technology Appraisal No. 53

Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine.

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This guidance is written in the following context:

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

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Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine

1. Guidance

- 1.1 Insulin glargine is recommended as a treatment option for people with type 1 diabetes.
- 1.2 Insulin glargine is not recommended for routine use for people with type 2 diabetes who require insulin therapy. Insulin glargine treatment should be considered only for those people with type 2 diabetes who require insulin therapy and who fall into one of the following categories.
 - Those who require assistance from a carer or healthcare professional to administer their insulin injections.
 - Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
 - Those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

This section (Section 1) constitutes the Institute's guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. The remainder of the document is structured in the following way:

2 Clinical need and practice	9 Review of guidance
3 The technology	Appendix A: Appraisal Committee
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7 Implementation and audit	
8 Related guidance	

A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0180.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0180 .

- 2.1 Diabetes is a chronic metabolic disorder caused by defects in insulin secretion and action. There are two major types of diabetes: type 1 and type 2.
- 2.2 In type 1 diabetes, the pancreas makes little or no insulin because the islet b cells, which produce insulin, have been destroyed through an autoimmune mechanism. Therefore, people with type 1 diabetes depend on insulin injections to survive.
- 2.3 Type 2 diabetes results from reduced insulin production and reduced tissue sensitivity to insulin (known as insulin resistance). Type 2 diabetes is a progressive disease in which insulin production declines as the disease progresses.
- 2.4 The age-standardised prevalence of diagnosed diabetes is estimated to be 2.23 per 100 males and 1.64 per 100 females. There are just over 1 million people in England and Wales with diagnosed diabetes. Of those, about 80% have type 2 diabetes (750,000 in England and 50,000 in Wales). The incidence of diabetes has been estimated at 1.7 new diagnoses per 1000 population per year (around 85,000 per year in England and 5000 per year in Wales).
- 2.5 Impaired insulin secretion results in increased levels of glucose in the blood (hyperglycaemia), which can, if prolonged, cause microvascular and macrovascular damage in the body. Common complications of diabetes include visual impairment, kidney failure, angina, myocardial infarction, stroke, foot ulceration and erectile dysfunction.
- 2.6 Two large landmark studies, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated the beneficial effects of maintaining good glycaemic control on the development and progression of diabetic complications in type 1 and type 2 diabetes respectively.
- 2.7 The principal goals of treatment for diabetes are to prevent acute and chronic complications and thus improve quality of life and avoid premature diabetes-associated death. These goals may be achieved through better control of blood glucose levels and through reductions in other macrovascular risk factors. In the assessment of diabetes management, the most important outcome measures are:
 - fasting blood/plasma glucose levels
 - the proportion of people who achieve target blood glucose levels; the target should reflect individual needs, but haemoglobin A1c (HbA_{1c}) levels of between 6.5% and 7.5% are generally recommended

- the prevention of acute episodes of hypoglycaemia and hyperglycaemia
- a reduction in other macrovascular risk factors, such as dyslipidaemia, high blood pressure and increased weight
- short-term quality of life, adverse events and treatment tolerance
- long-term effects on the incidence of diabetic complications, quality of life and mortality.

2.8 Type 2 diabetes can be managed through diet and exercise alone, at least in the early stages. However, it is a progressive disease, and nearly all individuals require oral antidiabetic drugs after some time. Most people eventually need insulin in order to maintain satisfactory blood glucose levels. Current treatment guidelines recommend a 'step-up' policy, starting with advice on diet and exercise, adding oral antidiabetic agents, first as monotherapy and then in combination, and finally using insulin if blood glucose control deteriorates.

2.9 Insulin is the mainstay of treatment for type 1 diabetes. There are four main types of insulin preparation: rapid-acting insulin analogues and short-acting insulins, meal-time insulin with a relatively fast onset of action; intermediate-acting insulins; and long-acting insulins, basal insulins with a slower onset and a longer duration of action. The most commonly used insulin regimens are twice-daily injections of a meal-time and basal insulin together, or four or five times daily injections comprising meal-time insulin before the main meals, and one or two injections of basal insulin (the meal-time+basal or basal-bolus regimen). The timing and frequency of insulin injections depend upon a number of factors, including the type of insulin, the amount and type of food eaten, the person's level of physical activity, experience of hyper- and hypo-glycaemia, the preference of the person and the appropriateness to his or her lifestyle. Other treatment options include insulin pump therapy, and pancreas and islet-cell transplantation.

2.10 The aim of the basal aspect of insulin administration is to provide a constant level of insulin between meals without increasing the risk of hypoglycaemia, particularly at night (nocturnal hypoglycaemia). The ideal insulin preparation for this role should have a flat profile of action (no pronounced peaks) and control glucose levels reproducibly, thus allowing consistent dosing.

2.11 In addition to the technology under consideration here, insulin glargine, there are currently two formulations of insulin used as basal therapy: ultralente and Neutral Protamine Hagedorn (NPH, also isophane insulin). NPH accounts for over 80% of the insulin currently prescribed for basal therapy in the UK.

2.12 NPH activity peaks 3–5 hours after administration; its duration of action is only 14 ± 3 hours and hence it has to be injected twice daily. With NPH administered at bedtime, peak insulin activity is reached while the glucose levels are low, which increases the risk of nocturnal hypoglycaemia. Nocturnal hypoglycaemia is accepted to be an important barrier to the achievement of optimal glucose control, as users tend to lower the insulin dose to prevent hypoglycaemia. Furthermore, NPH is a crystal suspension that should be mixed thoroughly before injecting – different degrees of mixing can lead to variable absorption from the injection site and hence variation in effect on blood sugar of similar insulin doses between individuals or at different times in the same individual.

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The technology

- 3.1 Insulin glargine (Lantus) is a long-acting human insulin analogue, which is prepared by modifying the chemical structure of insulin to allow more consistent release during the day, thereby mimicking natural basal insulin release. Insulin glargine is licensed for people with type 1 and type 2 diabetes where treatment with insulin is required.
- 3.2 Insulin glargine, injected subcutaneously, maintains a basal concentration of insulin in the blood that can be raised by supplementary injections of a short-acting insulin as required. Therefore, insulin glargine provides the basal component of basal–bolus insulin regimens. The prolonged absorption profile of insulin glargine, with no pronounced peaks over 24 hours, allows for once-daily dosing. Furthermore, as it does not require re-suspension prior to administration (because of its soluble formulation), it has the potential to reduce inter- and intra-user variability.
- 3.3 The cost of insulin glargine is £22.29–£26.00 per 1000 IU (excluding VAT; BNF September 2002) depending on the way the drug is packaged (for example, in vials, cartridges or pens). The annual cost of insulin glargine treatment is £203–£237 (excluding VAT) for type 1 diabetes, and £325–£380 for type 2 diabetes. These costs include the drug costs only, and they are based on a daily dose of 25 IU in people with type 1 diabetes and 40 IU in people with type 2 diabetes.

4

Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

- 4.1.1 Six fully published open-label randomised controlled trials (RCTs) were identified: four in type 1 and two in type 2 diabetes. The Assessment Report also reviewed seven studies published only in abstract form, and two unpublished abstracts that were made available by the manufacturer as part of its submission to the Institute. In addition, the manufacturer presented data from three observational studies.

Type 1 diabetes

- 4.1.2 Four fully published studies were identified evaluating the efficacy of insulin glargine in people with type 1 diabetes. All were open-label RCTs, two of them having partial blinding. All compared once-daily insulin glargine with once- or twice-daily NPH. In two trials, two different preparations of insulin glargine were compared with NPH as well as with each other. Individuals recruited into these trials all used a basal-bolus regimen to manage their blood glucose levels. In each study, insulin doses were titrated and adjusted in an attempt to achieve the target fasting blood glucose (FBG). This phase was followed by a post-titration period in which insulin doses were kept stable for each individual. The duration of the titration period and the proportion of the titration period relative to the whole study duration varied between studies. All studies used a measure of glycaemic control as the primary outcome measure, either FBG, fasting plasma glucose (FPG) or HbA_{1c}. The incidence and severity of hypoglycaemic episodes (classified as nocturnal, symptomatic or severe) were also reported.
- 4.1.3 In all four fully published studies, the mean change in FPG from baseline was significantly greater in the groups using insulin glargine compared with those using NPH. The difference between mean changes from baseline across the trials ranged between 1.34 mmol/litre and 2.23 mmol/litre. In three trials, insulin glargine was significantly superior to NPH in terms of reducing FBG (difference in mean change 0.71–1.50 mmol/litre); the fourth study showed no significant difference between insulin glargine and NPH for this endpoint.
- 4.1.4 Three of the four studies reported no statistically significant differences in HbA_{1c} between groups receiving insulin glargine and those receiving NPH. One study showed an overall statistically significant superiority of insulin glargine over NPH in terms of reducing HbA_{1c}. However, the duration of this trial was only 4 weeks. Therefore, this effect cannot be attributed solely to insulin glargine, as HbA_{1c} is a measure that reflects average glycaemic control over 6 to 8 weeks.
- 4.1.5 One study reported a significantly smaller percentage of people experiencing nocturnal hypoglycaemia in the insulin glargine groups taken together compared with the NPH group over the whole duration of the trial (36% versus 56% respectively; $p < 0.01$, $n = 333$). However, over the post-titration phase the difference was significant for only one glargine formulation compared with NPH (8% versus 19%, $p < 0.05$). In this study, there was a clear advantage of insulin glargine over NPH once daily in

reducing hypoglycaemia, but the percentages of individuals with nocturnal hypoglycaemia were very similar when insulin glargine was compared with NPH twice daily. One study reported fewer episodes of nocturnal hypoglycaemia in the group using insulin glargine compared with the group using NPH in the post-titration phase. One study showed no difference between insulin glargine and NPH in terms of the incidence of nocturnal hypoglycaemia. One study did not distinguish nocturnal hypoglycaemia from other hypoglycaemic episodes.

- 4.1.6 One study reported a smaller percentage of people experiencing symptomatic hypoglycaemia in the group using insulin glargine compared with the group using NPH for both the whole trial and the post-titration phases (40% versus 49% respectively for the post-titration phase only; figures were not reported for the whole trial). Two studies showed no difference between groups in the incidence of symptomatic hypoglycaemia in either the entire trial period or the post-titration phase. The fourth study did not distinguish symptomatic hypoglycaemia from other hypoglycaemic episodes.
- 4.1.7 Of the three studies reporting severe hypoglycaemia, only one reported that a significantly smaller percentage of people experienced severe episodes of hypoglycaemia in the insulin glargine group compared with the NPH group in the post-titration phase (1.9% versus 5.6% of patients respectively; $p < 0.05$). Two studies reported no significant differences between groups in terms of severe hypoglycaemia during either the entire trial period or the post-titration phase.

Type 2 diabetes

- 4.1.8 Two fully published open-label RCTs were identified which evaluated the efficacy of insulin glargine in people with type 2 diabetes. One trial recruited insulin-naïve individuals for whom oral antidiabetic agents had failed to establish adequate glycaemic control, and the other involved people who had been receiving insulin treatment for at least 3 months. Insulin doses were titrated throughout the studies – neither study included a basal–bolus regimen.
- 4.1.9 Neither study reported measurement of FPG. Only one study compared insulin glargine and NPH in terms of mean change in FBG from baseline – it found a non-significant difference. Both studies reported non-significant differences in the mean change in HbA_{1c} from baseline.

- 4.1.10 Both studies reported a significantly smaller percentage of people experiencing episodes of nocturnal hypoglycaemia in the treatment phase among those using insulin glargine compared with those using NPH (26% versus 35% in one study, n=518; the other trial did not report figures). In one trial, the difference was significant for the whole duration of the trial (35% versus 44% respectively; $p < 0.05$, n=518). Only one study compared once-daily NPH with insulin glargine; it showed a statistically significant difference in episodes of nocturnal hypoglycaemia in favour of insulin glargine, though as no figures are reported, it is difficult to interpret the clinical significance of this difference.
- 4.1.11 One study reported a smaller percentage of people experiencing episodes of symptomatic hypoglycaemia in the insulin glargine group compared with the NPH group for the post-titration phase (figures not reported), whereas the other study reported no significant difference in symptomatic hypoglycaemia between the groups during the entire study period (6.6% versus 10.4% respectively; $p > 0.05$, n=518). Neither study distinguished severe hypoglycaemia.

Observational studies

- 4.1.12 The analysis of a large observational dataset from Germany, which contains data on approximately 10,000 individuals and is managed by the manufacturer, showed a 1.7% reduction in HbA_{1c} levels in people with type 1 diabetes and a 1.4% reduction in people with type 2 diabetes compared with baseline when they were treated with insulin glargine for up to 8 weeks. Significance levels were not stated. In the same dataset, 70.3% of people with type 1 diabetes and 57.4% of people with type 2 diabetes reported fewer hypoglycaemic episodes when they were receiving insulin glargine. Another unpublished observational study using a US database (of 489 people with diabetes) reported a 0.36% reduction in HbA_{1c} levels compared with baseline in people with type 1 diabetes, and a 0.46% reduction in HbA_{1c} levels in people with type 2 diabetes when they were treated with insulin glargine for up to 6 months. Both figures were statistically significant. Hypoglycaemic episodes were not reported because of inconsistencies in the data. In addition, one abstract relating to an observational study was made available to the Institute in confidence by the manufacturer.

4.2 Cost effectiveness

- 4.2.1 No relevant economic evaluations were identified in the literature. The manufacturer's submission presented three separate economic models that evaluated the cost effectiveness of insulin glargine compared with NPH: one in people with type 1 diabetes who were previously on basal-bolus regimens, one in people with type 1 diabetes who were previously on premixed therapies, and one in people with type 2 diabetes. In addition, the Assessment Group developed its own models: one for type 1 diabetes and one for type 2 diabetes.
- 4.2.2 In the manufacturer's analysis, insulin glargine was estimated to be both more effective and less costly than the NPH-based regimens in people with type 1 diabetes who were previously on premixed therapies. The manufacturer estimated that the incremental cost-effectiveness ratios (ICER) for insulin glargine when compared with NPH were around £1200 per quality-adjusted life year (QALY) for people with type 1 diabetes who were previously on basal-bolus regimens, and between £4500 and £7000 per QALY for people with type 2 diabetes.
- 4.2.3 The Assessment Group concluded that the ICER values reported in the manufacturer's submission were significantly underestimated (that is, insulin glargine may be less cost effective than is suggested by the manufacturer's analysis) as most of the data used in the analysis would have biased the results in favour of insulin glargine. For example, the Assessment Report points out that the assumed reductions in HbA_{1c} levels (0.1% in people with type 2 diabetes and in those with type 1 diabetes who were previously on basal-bolus regimens and 1.8% in people with type 1 diabetes who were previously on premixed regimens), and hence in the rate of long-term complications, in groups using insulin glargine compared with groups using NPH do not seem to be supported by the published RCT evidence. Data used for estimating the episodes of hypoglycaemia were drawn from studies that showed the most favourable results for insulin glargine. Furthermore, the utility gain from reducing the fear of hypoglycaemia, which is the single parameter to which the model is most sensitive, was overestimated as much as ten-fold compared with the estimates provided in the Assessment Report.

4.2.4 The Assessment Group's analysis estimated that the ICERs for insulin glargine when compared with NPH were around £32,000 per QALY for type 1 diabetes and around £120,000 for type 2 diabetes for the base-case scenarios. The Assessment Group's analyses were most sensitive to the changes in utility gains from reducing the fear of hypoglycaemia.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the evidence on both the clinical effectiveness and the cost effectiveness of insulin glargine, having considered evidence from people with diabetes who require insulin therapy, those who represent them, and clinical experts, on the nature of the condition and the value placed by users on the effects of insulin glargine treatment. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

4.3.2 The Committee recognised the value of research evidence from both RCT and observational sources, bearing in mind the strengths and weaknesses of different study designs. The Committee was also aware of the implications of the inverse relationship between the frequency of hypoglycaemic episodes and HbA_{1c} levels, wherein an increased frequency of hypoglycaemic episodes paradoxically reduces the HbA_{1c} level.

4.3.3 The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' 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. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life.

4.3.4 The Committee accepted that a once-daily insulin injection that could ensure a flat pharmacokinetic profile of basal blood insulin throughout the day would improve the quality of life of individuals. Firstly, it would provide more flexibility in their lifestyle by the avoidance of peaks and troughs in insulin levels.

Secondly, it would reduce the potential for symptomatic hypoglycaemic attacks and concerns over the correct balance of glycaemic control as indicated in 4.3.3.

- 4.3.5 The Committee understood that the wide range of cost-effectiveness estimates (presented in Section 4.2) was mainly reflective of the different utility values attached to 'fear of hypoglycaemia' in each analysis, as well as the way the number of hypoglycaemic episodes avoided was calculated and the impact of insulin glargine on HbA_{1c} levels.
- 4.3.6 During the course of the appraisal, the manufacturer revised its estimates of utility gain per hypoglycaemic episode avoided (to 0.0052) and acquisition cost of insulin glargine. The Committee, therefore, considered a revised cost-effectiveness analysis, using these figures. The revised analysis used the manufacturer's estimates of the cost of treating episodes of severe hypoglycaemia (£218) and the data from the study that showed the most favourable results in terms of reduction of number of hypoglycaemic episodes.
- 4.3.7 Taking these factors into account, the Committee considered it likely that when insulin glargine was assumed only to reduce the episodes of hypoglycaemia but not to improve HbA_{1c} levels, the ICER for insulin glargine treatment versus NPH would be a base-case figure of around £3500 per QALY for type 1 diabetes and £32,500 per QALY for type 2 diabetes. When insulin glargine was assumed to improve HbA_{1c} levels but to have no effect on the number of hypoglycaemic episodes, the ICERs were estimated to be around £16,000 per QALY for type 1 diabetes and £72,000 per QALY for type 2 diabetes.
- 4.3.8 On the balance of effectiveness and cost-effectiveness evidence, the Committee concluded that insulin glargine should be recommended as a treatment option in people with type 1 diabetes who require insulin.
- 4.3.9 The Committee considered that the cost effectiveness of insulin glargine was less well established for people with type 2 diabetes, principally because of the lower frequency of hypoglycaemic episodes among this group compared with those with type 1 diabetes and consequently the relatively limited scope for improvement (in terms of absolute numbers of avoided hypoglycaemic episodes) as documented in the clinical studies.

4.3.10 The Committee concluded that it would be more cost effective to target the use of insulin glargine to those people with type 2 diabetes who would be most likely to benefit (identified in Section 1.2). Principally, this is because insulin glargine would potentially offer a significant improvement in quality of life to these groups of individuals, either due to a reduced number of severe hypoglycaemia episodes, or fewer daily injections of insulin. In addition, the Committee accepted that, on the balance of probabilities, the health care resources spent on those who require assistance with their insulin injections, would be reduced significantly (mainly in terms of the time spent by health care professionals to give the injections) to the extent that the use of insulin glargine in this group is likely to be cost-effective.

5

Further research

5.1 Further good-quality studies are needed to investigate the following:

- The degree to which individuals' 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.
- The duration and severity profile of hypoglycaemic episodes, which may differ between individuals. It is also recommended that the method of documenting hypoglycaemic episodes in future clinical studies in this area is improved (to include the duration of the episode and time of the day in which the episode occurred) to allow the impact on quality of life to be better appreciated.
- The effectiveness and cost effectiveness of insulin glargine as part of a multiple-daily-injection regimen compared with insulin pump therapy.

6

Implications for the NHS

6.1 The impact of insulin glargine on the NHS budget will depend on the epidemiology of the target population, the cost of insulin glargine and the expected uptake rates for insulin glargine.

6.2 It is estimated that up to 137,000 individuals would be eligible for insulin glargine treatment. This is based on the following assumptions:

- the age-standardised prevalence of diagnosed diabetes is 2.23 per 100 males and 1.64 per 100 females
- type 2 diabetes constitutes 80% of all diabetes

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Implementation and audit

- all people with type 1 diabetes and 30% of people with type 2 diabetes require insulin, and of those, 50% of people with type 1 and 15% of people with type 2 require a basal-bolus regimen.
- 6.3 If the incremental cost of insulin glargine (based on vial costs) is assumed to be £101 per annum for people with type 1 diabetes (annual cost of insulin glargine is £203 and annual cost of NPH is £102), and £162 per annum for people with type 2 diabetes (annual cost of insulin glargine is £325 and annual cost of NPH is £163), the cost of switching all potentially eligible individuals to insulin glargine would cost the NHS around £16 million per annum. The actual cost to the NHS would be proportionally less depending on the uptake of this technology.
- 7.1 NHS Trusts, consultants treating people with diabetes and general practitioners should review policies and practices regarding the treatment of people with diabetes to take account of the guidance set out in Section 1.
- 7.2 Local guidelines or care pathways on the care of people with diabetes should incorporate the guidance in Section 1.
- 7.3 To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix D.
- 7.3.1 Insulin glargine is a treatment option for people with type 1 diabetes.
- 7.3.2 Insulin glargine is considered for an individual with type 2 diabetes only if he or she requires insulin therapy and falls into one of the following categories.
- The individual requires assistance from a carer or healthcare professional to administer insulin injections.
 - The individual's lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
 - The individual would otherwise use twice-daily basal insulin injections in combination with oral antidiabetic drugs.
- 7.4 Local clinical audits also could include assessment of compliance with the standards in the National Service Framework for Diabetes.

8.1 The Institute has issued guidance on the use of rosiglitazone and pioglitazone for type 2 diabetes. It is also publishing a series of guidelines on the management of type 2 diabetes.

- National Institute for Clinical Excellence (August 2000) Guidance on the use of rosiglitazone for type 2 diabetes mellitus. *NICE Technology Appraisal Guidance No. 9*. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk.
- National Institute for Clinical Excellence (March 2001) Guidance on the use of pioglitazone for type 2 diabetes mellitus. *NICE Technology Appraisal Guidance No. 21*. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk.
- National Institute for Clinical Excellence (February 2002) Management of type 2 diabetes: retinopathy – screening and early management. *Inherited Guideline E*. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk.
- National Institute for Clinical Excellence (February 2002) Management of type 2 diabetes: renal disease – prevention and early management. *Inherited Guideline F*. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk.
- National Institute for Clinical Excellence (September 2002) Management of type 2 diabetes: management of blood glucose. *Inherited Guideline G*. London: National Institute for Clinical Excellence.
- National Institute for Clinical Excellence (October 2002) Management of type 2 diabetes: management of blood pressure and blood lipids. *Inherited Guideline H*. London: National Institute for Clinical Excellence.

8.2 The following technology appraisals and clinical guidelines are part of the Institute's ongoing work programme.

- Patient education models for diabetes – due to be issued early 2003 (technology appraisal).
- Insulin pumps – due to be issued early 2003 (technology appraisal).
- Management of type 2 diabetes: foot care – due to be issued late 2003 (update of an existing clinical guideline published by the Royal College of General Practitioners).
- Type 1 diabetes: diagnosis and management of type 1 diabetes in primary and secondary care – due to be issued early 2004 (clinical guideline).

9.1 The guidance on this technology is reviewed in November 2005.

Andrew Dillon
Chief Executive

December 2002

Appendix A

Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members appears below. The Appraisal Committee meets twice a month other than in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and topics are not moved between the branches.

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

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

Dr Jane Adam

Radiologist, St George's Hospital,
London

Professor R L Akehurst

Dean, School of Health Related
Research, Sheffield University

Dr Sunil Angris

General Practitioner, Waterhouses
Medical Practice

Professor David Barnett (Chair)

Professor of Clinical Pharmacology,
University of Leicester

Professor Sir Colin Berry

Retired Professor of Morbid Anatomy
& Histopathology, The Royal London
Hospital

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Professor Carol Black

(resigned June 2002)
Consultant Physician, Royal Free
Hospital & UCL, London

Professor John Brazier

Health Economist, University of
Sheffield

Professor Rosamund Bryar

Professor of Community and Primary
Care Nursing, St Bartholomew School
of Nursing and Midwifery

Professor Martin Buxton

Director of Health Economics Research
Group, Brunel University

Professor Mike Campbell

Statistician, Institute of General
Practice & Primary Care, Sheffield

Dr Karl Claxton

Health Economist, University of York

Professor Sarah Cowley

Professor of Community Practice
Development, Kings College, London

Professor Sarah Cowley

Professor of Community Practice
Development, Kings College, London

Professor Nicky Cullum

(resigned January 2002)
Professor in Health Sciences/Director -
Centre for Evidence Based Nursing,
University of York

Dr Mike Davies

Consultant Physician, University
Department of Medicine and
Metabolism, The Manchester Royal
Infirmary

Professor Jack Dowie

Health Economist, London School of
Hygiene

Mr Chris Evennett

(resigned June 2002) Chief Executive,
Mid-Hampshire Primary Care Trust

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust

Professor Terry Feest
Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry

Professor Gary A Ford
Professor of Pharmacology of Old Age / Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Mrs Sue Gallagher
Former Chief Executive, Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust

Mr John Goulston
Director of Finance, Barts and the London NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Clinical Reader in Surgery, University of Oxford

Professor Philip Home
Professor of Diabetes Medicine, University of Newcastle

Dr Terry John
General Practitioner, The Firs, London

Dr Diane Ketley
(term of office ended August 2002)
Research into Practice Programme Leader, NHS Modernisation Agency

Dr Mayur Lakhani
(term of office ended August 2002)
General Practitioner, Highgate Surgery, Leicester, and Lecturer, University of Leicester

Ruth Lesirge
Lay Representative, previously Director, Mental Health Foundation

Dr George Levvy
Lay Representative, Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
Chief Executive, NHS Confederation

Professor Miranda Mugford
Health Economist, University of East Anglia

Mr M Mughal
Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust

Mr James Partridge
Lay Representative, Chief Executive, Changing Faces

Siân Richards
Chief Executive, Cardiff Local Health Board

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales

Dr Rhiannon Rowsell
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Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens (Vice-Chair)
Professor of Public Health, University of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital, Salford

Dr Cathryn Thomas
General Practitioner, and Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Senior Lecturer and Public Health Consultant, University of Southampton

Dr David Winfield
Consultant Haematologist, Royal Hallamshire Hospital

Appendix B

Sources of evidence considered by the Committee

The following documentation and opinion were made available to the Committee:

A. Assessment Report prepared by: School of Health and Related Research University of Sheffield

The Clinical and Cost-effectiveness of Long-acting Insulin Analogue, Insulin Glargine, June 2002

B. Manufacturer/sponsor submissions:

- Aventis

C. Professional/specialist and patient/carer group submissions:

- Association of British Clinical Diabetologists, British Geriatrics Society, Diabetes UK (specialist section) and the Royal College of Physicians
- British Dietetic Association
- British Society for Paediatric Endocrinology and Diabetes and the Royal College of Paediatrics and Child Health
- Department of Health and Welsh Assembly Government
- Diabetes UK
- Health Technology Board for Scotland
- Royal College of General Practitioners
- Royal College of Nursing

D. Expert perspectives:

- Will Anderson on behalf of Diabetes UK
- Professor Anthony Barnett, Consultant Physician, Birmingham Heartlands Hospital
- Dr Ian Gallen, Consultant Physician, Wycombe General Hospital
- Peter McKeown, Diabetes Campaigners Networks Manager, Diabetes UK
- Lindsay Oliver, Lead Diabetes Dietician, Diabetes Resource Centre, North Tyneside General Hospital
- Professor David Owens, Professor of Diabetes, Llandough Hospital

Appendix C

Patient information

Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0181 for the English patient leaflet and N0182 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance for both the NHS and patients on the use of medicines, medical equipment, diagnostic tests and clinical and surgical procedures and under what circumstances they should be used.

To produce this guidance, NICE looks at how well the medicine, equipment or procedure works and also how well it works in relation to how much it costs. This process is called an appraisal. The appraisal process involves the manufacturer of the medicine or equipment for which guidance is being produced and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Each appraisal takes about 12 months to complete.

NICE was asked to look at the available evidence on a type of medicine for diabetes that works like insulin in the body but which has been made in such a way that its effects in the body are quite long-lasting – this type of medicine is called a long-acting insulin analogue. NICE has specifically been asked to look at the long-acting insulin analogue called insulin glargine and provide guidance that will help the NHS in England and Wales decide when it should be used.

What is diabetes?

Diabetes is a condition in which the body's pancreas does not produce enough insulin, or produces insulin but cannot use it properly. Insulin is a substance that controls the amount of glucose (sugar) in the blood by co-ordinating its use by different parts of the body (such as the muscles). As the effect of insulin is to reduce the amount of glucose in the blood, if there isn't enough insulin or it isn't having the proper effect, the level of glucose in the blood increases – this can have harmful effects both in the short and long term.

There are two types of diabetes: type 1 and type 2.

Type 1 diabetes occurs when there is a severe lack of insulin in the body because most or all of the cells in the pancreas that produce it have been destroyed. This type of diabetes usually appears in people under 40, often during childhood, and is treated by insulin injections and diet.

Type 2 diabetes develops when the body can still make some insulin, but not enough for its needs, or when the insulin that is produced does not work properly (this is also known as insulin resistance). This type of diabetes usually appears in people over the age of 40, though it can appear in younger people.

People with type 2 diabetes usually start to manage their glucose levels by making changes to their diet and lifestyle. But type 2 diabetes tends to get worse with time as less and less insulin is made or the insulin that is made becomes less and less effective, so most people eventually have to start taking one or more medicines. One of the options when blood glucose is becoming difficult to control is to use insulin or a medicine that acts like insulin in the body.

What is insulin glargine?

Insulin glargine is a medicine that has the same effect as insulin in the body. It has been made in such a way that one injection works over 24 hours to provide a constant 'background' level or 'basal level' of insulin. In order to deal with the high amounts of glucose that enter the blood after a meal, a person taking a medicine such as insulin glargine would also have injections of a different type of insulin or insulin-like medicine at meal-times.

Insulin glargine is produced in a dissolved form, so there's no need for the user to mix it before injecting it. This is thought to make it more likely that the same amount of insulin is delivered every time. Insulin glargine is licensed for use in people with type 1 diabetes and in people with type 2 diabetes who need insulin.

What is a hypoglycaemic episode?

A hypoglycaemic episode happens when the blood glucose level becomes too low, with the result that the person may become anxious, dizzy or disoriented. If the blood glucose level becomes very low, the person may have convulsions or become unconscious. Hypoglycaemic episodes can happen if there's too much insulin or insulin-like medicine in the blood. This is why it's important, for example, that the background insulin level remains constant and doesn't increase unless there's also an increase in the amount of glucose in the blood (after a meal).

What has NICE recommended?

NICE has recommended insulin glargine as an option for people with type 1 diabetes. For people with type 2 diabetes who need to take insulin, NICE has recommended that insulin glargine should be an option only if the person:

- needs help with his or her insulin injections from a carer or healthcare professional, or
- has repeated and unpleasant hypoglycaemic episodes (see above) that significantly affect his or her way of life, or

- would otherwise need to have two insulin injections to maintain background levels every day as well as having to take other diabetes medicines orally.

What should I do next?

If you or someone you care for has diabetes, you should discuss this guidance with your doctor.

Will NICE review its guidance?

Yes. The guidance will be reviewed in November 2005.

Further information

The NICE website (www.nice.org.uk) has further information on NICE and the full guidance on the use of long-acting insulin analogues to treat diabetes that has been issued to the NHS. The guidance can also be requested from the NHS Response Line by phoning 0870 1555 455 and quoting reference N0179.

If you have access to the Internet, you can find more information about diabetes on the NHS Direct website (www.nhsdirect.nhs.uk). You can also phone NHS Direct on 08 45 46 47.

Appendix D

Detail on criteria for audit of the use of long acting insulin analogues for the treatment of diabetes

Possible objectives for an audit

An audit on the use of insulin glargine could be carried out to ensure that the treatment is not being used inappropriately.

Possible patients to be included in the audit

An audit could be carried out on all patients who have been prescribed insulin glargine in a reasonable time period, for example, the last year, to ensure that these patients meet criteria for the use of the treatment.

Measure that can be used as a basis for audit

The measure that can be used in an audit of patients who have been prescribed insulin glargine is as follows.

Criterion	Standard
1. The patient has type 1 diabetes or the patient has type 2 diabetes and requires insulin therapy and falls into one of the following categories: a. requires assistance to administer insulin injections, or b. has a lifestyle that is significantly restricted by recurrent symptomatic hypoglycaemic episodes, or c. would otherwise use twice-daily basal insulin injections in combination with oral antidiabetic drugs.	100% of patients for whom insulin glargine is prescribed

Calculation of compliance with the measures

Compliance with the measure described in the table is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion plus the number of patients who meet any exception that might be agreed locally}}{\text{Number of patients to whom the measure applies.}} \times 100$$

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Exception	Definition of Terms
None	Local clinicians will have to agree on how to define restriction of lifestyle and how the decision that the patient requires assistance to administer insulin injections is likely to be documented for audit purposes



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