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E Warren, E Weatherley-Jones, J Chilcott and C Beverley

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# Abstract

## Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine

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**Objectives:** To evaluate the use of insulin glargine in its licensed basal-bolus indication in terms of both clinical and cost-effectiveness.
**Data sources:** Electronic databases.
**Review methods:** A systematic review of the literature, involving a range of databases, was performed to identify all papers relating to insulin glargine.
**Results:** Nineteen studies met the inclusion criteria but full reports were available for only six. For type 1 diabetes patients, insulin glargine appears to be more effective than neutral protamine Hagedorn (NPH) in reducing fasting blood glucose (FBG) but not in reducing glycosylated haemoglobin ($HbA_{1c}$) and there is some evidence that both insulins are as effective as each other in both FBG and $HbA_{1c}$ control. For type 2 patients for whom oral antidiabetic agents provide inadequate glycaemic control, there is no evidence that insulin glargine is more effective than NPH in reducing either FBG or $HbA_{1c}$ and some evidence that both insulins are as effective as each other in both FBG and $HbA_{1c}$ control. Evidence for control of hypoglycaemia is equivocal. In studies where insulin glargine is demonstrated to be superior to NPH in controlling nocturnal hypoglycaemia, this may be only apparent when compared with once-daily NPH and not twice-daily NPH. Further, this superiority of glargine over NPH in the control of nocturnal hypoglycaemia may relate to one formulation of insulin glargine (HOE901[80]) and not another (HOE901[30]). There is no conclusive evidence that insulin glargine is superior to NPH in controlling symptomatic hypoglycaemia and severe hypoglycaemia. Insufficient data are available to conclude whether insulin glargine is different from each of the commonly used NPH dosing regimens: once daily and more than once daily. Given the lack of a published evidence base for the cost-effectiveness of insulin glargine, the economic review concentrates on a review of the industry submission and an amended model. Three economic models are provided in the submission, two relating to type 1 diabetes and one relating to type 2 diabetes. All three models compare the cost–utility of insulin glargine against NPH insulin. In general, the structures of the models are poor and in all three models, mistakes relating to assumptions and calculations have been made. The assessment team believe that the cost per QALY estimates generated by the Aventis model may be an underestimate for several reasons. The cost-effectiveness of insulin glargine in both type 1 and type 2 diabetes is highly sensitive to the amount of utility associated with reducing the fear of hypoglycaemia.
**Conclusions:** The evidence suggests that, compared with NPH insulin, insulin glargine is effective in reducing the number of nocturnal hypoglycaemic episodes, especially when compared with once-daily NPH. There appears to be no improvement in long-term glycaemic control and therefore insulin glargine is unlikely to reduce the incidence of the long-term microvascular and cardiovascular complications of diabetes. Further research into insulin glargine is needed that addresses the quality of life issues associated with fear of hypoglycaemia and also the economic impact of balance of $HbA_{1c}$ control and incidence of hypoglycaemia achieved in practice. Studies examining the economic evidence on insulin glargine should be published.



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# Contents

# List of abbreviations

| | |
|---|---|
| CCTR | Cochrane Controlled Trials Register |
| CDSR | Cochrane Database of Systematic Reviews |
| CVD | cardiovascular disease |
| DARE | Database of Abstracts of Reviews of Effectiveness |
| DARTS | Diabetes Audit and Research in Tayside Scotland |
| DCCT | Diabetes Control and Complications Trial |
| DKA | ketoacidosis diabetic coma |
| DQOL | diabetes quality of life measure |
| FBG | fasting blood glucose |
| FPG | fasting plasma glucose |
| GDM | gestational diabetes mellitus |
| $HBA_{1c}$ | glycosylated haemoglobin |
| HRG | Healthcare Resource Group |
| IDDM | insulin-dependent diabetes mellitus |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| NHS EED | NHS Economic Evaluations Database |
| NICE | National Institute for Clinical Excellence |
| NIDDM | non-insulin-dependent diabetes mellitus |
| NPH | neutral protamine Hagedorn |
| OGTT | oral glucose tolerance test |
| OHE HEED | OHE Health Economic Evaluations Database |
| PG | plasma glucose |
| QALY | quality-adjusted life-years |
| RCT | randomised controlled trial |
| ScHARR | School of Health and Related Research |
| SCI | Science Citation Index |
| UKPDS | UK Prospective Diabetes Study |
| WHO | World Health Organization |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



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# Executive summary

## Objectives

The aim of this review was to evaluate the use of insulin glargine in its licensed basal-bolus indication in terms of both clinical and cost-effectiveness.

## Methods

A systematic review of the literature, involving a range of databases, was performed to identify all papers relating to insulin glargine.

## Results

### Number and quality of studies

Nineteen studies met the inclusion criteria but full reports were available for only six.

### Clinical effectiveness

For type 1 diabetes patients, insulin glargine appears to be more effective than neutral protamine Hagedorn (NPH) in reducing fasting blood glucose (FBG) but not in reducing glycosylated haemoglobin ($HbA_{1c}$) and there is some evidence that both insulins are as effective as each other in both FBG and $HbA_{1c}$ control. For type 2 patients for whom oral antidiabetic agents provide inadequate glycaemic control, there is no evidence that insulin glargine is more effective than NPH in reducing either FBG or $HbA_{1c}$ and some evidence that both insulins are as effective as each other in both FBG and $HbA_{1c}$ control.

Evidence for control of hypoglycaemia is equivocal. In studies where insulin glargine is demonstrated to be superior to NPH in controlling nocturnal hypoglycaemia, this may be only apparent when compared with once-daily NPH and not twice-daily NPH. Further, this superiority of glargine over NPH in the control of nocturnal hypoglycaemia may relate to one formulation of insulin glargine (HOE901[80]) and not another (HOE901[30]). There is no conclusive evidence that insulin glargine is superior to NPH in controlling symptomatic hypoglycaemia and severe hypoglycaemia. Insufficient data are available to conclude whether insulin glargine is different from each of the commonly used NPH dosing regimens: once daily and more than once daily.

### Health economics

There are no published economic studies on insulin glargine or indeed NPH insulin. An economic evaluation of insulin glargine has been provided in the Aventis submission. Given the lack of a published evidence base for the cost-effectiveness of insulin glargine, the economic review concentrates on a review of the industry submission and an amended ScHARR model. Three economic models are provided in the submission, two relating to type 1 diabetes (previously on other basal-bolus regimes or previously on premix therapies) and one relating to type 2 diabetes. All three models compare the cost–utility of insulin glargine against NPH insulin. In general, the structures of the models are poor. In all three models, mistakes relating to assumptions and calculations have been made. The industry submission concludes that insulin glargine is highly cost-effective in all three models. The incremental cost per quality-adjusted life year (QALY) ratios generated by the company models are presented in the first table.

Based on the evidence presented, there appears to be no rationale for the two separate models within type 1 diabetes. No evidence has been presented that suggests type 1 patients previously receiving

*Cost per QALY results provided in the Aventis submission*

| Model | Base-case cost per QALY (£) | Cost per QALY range (£) |
|---|---|---|
| Type 1 (other basal-bolus) | 1,148–1,292 | 792–45,853 |
| Type 1 (premix) | Dominant | Dominant–9,509 |
| Type 2 | 4,552–7,169 | 3,887–308,105 |



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*Cost per QALY results estimated by ScHARR*

| Patient group | Base-case cost per QALY[a] (£) | Cost per QALY range (£) |
|---|---|---|
| Type 1 | 3,496–4,978 | 954–554,411 |
| Type 2 | 32,508–43,411 | 6,168–10,214,864 |

[a] Cost per QALY ratio depends on the method on administration (vial, cartridge or insulin pen).

premix therapies would experience better glycaemic control on insulin glargine than patients previously treated by other basal-bolus regimes.

An evaluation of the industry model was made and a separate model was constructed. The assessment team believe that the cost per QALY estimates generated by the Aventis model may be an underestimate for several reasons:

*Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The incremental cost per QALY ratios generated from the assessment team models are presented in the second table.

The cost-effectiveness of insulin glargine in both type 1 and type 2 diabetes is highly sensitive to the amount of utility associated with reducing the fear of hypoglycaemia. The industry submission explores this issue through a number of analyses and the claimed base case is based on the most favourable of these analyses. By changing this assumption, the cost per QALY ranges from cost-effective to not cost-effective.

## Conclusions

The evidence suggests that, compared with NPH insulin, insulin glargine is effective in reducing the number of nocturnal hypoglycaemic episodes, especially when compared with once-daily NPH. There appears to be no improvement in long-term glycaemic control and therefore insulin glargine is unlikely to reduce the incidence of the long-term microvascular and cardiovascular complications of diabetes.

## Recommendations for further research

Further research into insulin glargine is needed in these key areas:

- Quality of life associated with fear of hypoglycaemia.
- Economic impact of balance of $HbA_{1c}$ control and incidence of hypoglycaemia achieved in practice. Studies examining the economic evidence on insulin glargine should be published.

# Chapter 1

## Aim of the review

The aim of this review is to evaluate the incremental clinical and cost-effectiveness of insulin glargine, a long-acting insulin analogue, compared with existing basal-bolus insulin treatments.

Specific objectives are:

- To evaluate the relative clinical effectiveness, in terms of glycaemic control and the incidence of hypoglycaemic events.
- To estimate the relative clinical effectiveness in terms of prevention of the longer term complications of diabetes mellitus.
- To estimate the relative effect on overall mortality and quality of life adjusted mortality.
- To estimate the incremental cost-effectiveness of insulin glargine in comparison with conventional therapy.
- To estimate the possible cost impact on the NHS in England and Wales.

The report is based upon an assessment of insulin glargine undertaken on behalf of the National Institute for Clinical Excellence (NICE) and incorporates changes made in response to information made available and comments made during the NICE consultation process. The report collates the original report to NICE and an addendum, both of which are available separately on the NICE website at http://www.nice.org.uk.



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# Chapter 2
# Background

## Description of underlying health problem

### Definition of diabetes mellitus

Diabetes mellitus is a group of chronic disorders characterised by elevated blood glucose levels (hyperglycaemia). This is a consequence of inadequate control of glucose in the blood by the pancreatic hormone insulin and/or abnormal resistance to insulin. A more specialised definition by the WHO is given below.

The WHO defines diabetes mellitus as "a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both".[1]

Glucose is the principal energy source for cellular metabolism and efficient metabolism depends on an optimum blood glucose concentration. Insulin is secreted by $\beta$ cells in the islets of Langerhans of the pancreas. Normally, the concentration of insulin in the blood increases in response to an elevation in blood glucose levels that occur naturally after eating. The action of insulin on a number of cells, including muscle and fat cells, results in absorption of glucose out of the blood, thus maintaining blood glucose levels within the normal range. Hyperglycaemia results from a total or partial lack of insulin available or ineffectual for this function. The potential consequences of hyperglycaemia are damage to many of the body's systems, in particular the blood vessels and nerves. Loss of glycaemic control is associated with long-term complications and people with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.[2]

There are two main aetiological types of diabetes:

**Type 1 diabetes mellitus** [previously termed insulin-dependent diabetes mellitus (IDDM)] is a condition in which the pancreas makes little or no insulin because the islet $\beta$ cells have been destroyed through an autoimmune mechanism. The insulin-dependent tissues are less able to take up glucose and therefore there is a build-up of glucose in the body.

**Type 2 diabetes mellitus** [previously termed non-insulin-dependent diabetes mellitus (NIDDM)] is caused by two factors: the reduction in insulin production and the presence of insulin resistance in skeletal muscle and liver. Type 2 diabetes is a progressive disease in which insulin production declines as the disease progresses, resulting in increasing failure of glucose absorption. In early stages of type 2 diabetes, the most significant pathology is insulin resistance. Insulin resistance develops from unknown genetic defects combined with environmental factors, predominantly obesity and physical inactivity.[3] As the disease progresses, insulin resistance remains relatively stable and insulin production declines progressively.

The labels IDDM and NIDDM were previously used for type 1 and 2 diabetes, respectively. However, these labels may be misleading and are no longer recommended, because patients with type 2 disease may take injected insulin.

In addition to type 1 and 2 diabetes, the WHO classification system includes a number of other aetiological types:

- other specific types
- genetic defects of islet $\beta$ cell function
- genetic defects in insulin action
- diseases of the exocrine pancreas
- endocrinopathies
- drug or chemical-induced diabetes
- uncommon forms of immune-mediated diabetes
- other genetic syndromes associated with diabetes
- gestational diabetes mellitus (GDM) (diagnosed during pregnancy).

Individuals with diabetes mellitus may be further subdivided according to treatment, as follows:

- patients not requiring insulin
- patients who use insulin in order to control blood glucose levels
- patients who require insulin for survival.

The criteria for the diagnosis of diabetes in non-pregnant adults are as follows:

- symptoms of diabetes and a casual plasma glucose (PG) $\geq$ 200 mg/dl (11.1 mmol/l).



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Casual is defined as any time of day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss. Or:

- Fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/l). During the test, a sample of blood is obtained following a period of not eating or drinking (except water) for at least 8 hours. Or:
- 2-hour PG ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). During the test, a fasting blood sugar is obtained initially. The person is then asked to drink a sweet, sugary beverage (75 g of anhydrous glucose dissolved in water). Blood glucose levels are then obtained every 30 minutes for the next 2 hours. A blood glucose level <140 mg/dl at 2 hours is considered normal. A blood glucose level of >200 mg/dl at 2 hours is indicative of diabetes. A blood glucose level of 140–200 mg/dl at 2 hours indicates impairment of glucose tolerance.

Three ways to diagnosis diabetes are available and each must be confirmed on a subsequent day. FPG is the preferred test because of its lower cost and ease of use. Hyperglycaemia not sufficient to meet the diagnostic criteria for diabetes is categorised as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on whether it is identified through an FPG or an OGTT. Both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease (CVD).

## Symptoms and complications

The main symptoms of diabetes are the following:

- unexplained weight loss (although appetite often increases)
- polyphagia (frequently hungry)
- polyuria (frequently urinating)
- polydipsia (frequently thirsty)
- blurred vision
- severe fatigue
- poor wound healing (cuts, scrapes, etc.)
- dry or itchy skin
- recurrent infections such as vaginal yeast infections, groin rash or external ear infections (swimmers' ear).

The main complications of diabetes are the following:

- Arteriosclerosis (hardening of the arteries), which can also lead to stroke and other heart conditions. Arteriosclerosis refers to the build-up of plaque in the walls of the arteries, leading to a reduction in the calibre of the vessel. The narrowing does not occur suddenly but builds up over several years. The result is that the arteries become constricted, their elasticity disappears and the volume of blood able to travel through them at any given time is reduced.
- Diabetic kidney disease. Diabetic kidney disease is caused mainly by high blood glucose levels. Due to damage in the small blood vessels in the kidneys, protein is released into the urine. Diabetic kidney disease is often associated with high blood pressure, which might not develop until after the kidneys have been affected.
- Diabetic retinopathy (diabetes-related eye disease). Diabetic retinopathy is an eye disease generally associated with long-standing diabetes. It is a major cause of poor vision in the UK and, if left untreated, diabetic retinopathy can lead to blindness. Prolonged periods of high blood sugar levels cause damage to the small blood vessels in the retina at the back of the eye. These blood vessels initially become leaky and may then become blocked off. The leakiness causes haemorrhages (small spots of blood) and exudates (leakage of fats) from the vessels on to the retina. The leakage may also cause swelling (oedema of the retina). The blocked vessels can starve the retina of oxygen, which leads to the growth of new abnormal vessels from the retina.
- Diabetic neuropathy (degradation of the nerves), leading to foot ulceration and infection. This condition can either be acute or chronic. The neuropathy can affect the nervous system, either as a painful or reduced sense of touch, muscle function (motor control) or the inner organs and blood vessels (the autonomic system). Diabetic neuropathy is caused by a prolonged high blood glucose level. Once the blood glucose level rises above a certain point, the nerves throughout the body gradually begin to be damaged.
- Gangrene in the legs.
- Susceptibility to infections, for example, urinary tract infections.
- High blood sugar levels, leading to ketoacidosis.
- Ketoacidosis (diabetic coma) (DKA) is loss of consciousness due to untreated or under-treated diabetes.

Severe high blood sugars and ketoacidosis are serious and potentially life-threatening medical problems that can occur in diabetes. High blood sugars become life threatening in type 1 or insulin-dependent diabetes only when that person does not receive enough insulin from injections or

an insulin pump. This can be caused by skipping insulin or not receiving enough insulin when large amounts are required owing to an infection or other major stress.

The most important factors in reducing one's risk of developing the complications associated with diabetes include maintaining tight blood glucose control and having regular check-ups by a physician. Patients with type 1 diabetes run a greater risk of other health problems; however, studies have shown that many of these problems can be prevented or successfully treated when they are identified early.

## Epidemiology

Diabetes mellitus affects 2.4% of adult population,[4] of whom 200,000 have type 1 diabetes and more than a million have type 2 diabetes.[5] Without taking into account improved detection, the prevalence of both type 1 and type 2 diabetes will increase over the next two decades. Type 2 diabetes is more common in the elderly population, is also more prevalent in men than women and varies depending on the ethnic group. It has been estimated that the prevalence of type 2 diabetes in the UK will more than double between 1997 and 2010.[6] Diabetes is much more common in people of Asian Indian and Afro-Caribbean origin. In a Newcastle study,[7] 17.9% of South Asians aged 25–74 years were found to have the disorder, with a further 18.7% having impaired glucose tolerance, which implies a 30–50% higher risk of the development of diabetes in 5–10 years. Weight is another major risk factor for type 2 diabetes. It is estimated that 75% of people who develop type 2 diabetes are, or have been, obese.

## Morbidity and mortality

Diabetic complications are a major cause of morbidity:[4]

- Diabetes is associated with a 2–3-fold increase in the risk of coronary heart disease and stroke.
- Diabetic retinotherapy is the commonest cause of blindness in people of working age.
- About 15% of people with diabetes develop foot ulcers, and 5–15% of people with diabetic foot ulcers need amputations.

Estimates of diabetes-related mortality based on death certificate data are seriously misleading, because diabetes will have been a contributory factor in many deaths attributed to other underlying causes. Age- and sex-specific mortality rates are higher for people with diabetes than for non-diabetic individuals.[8]

## Current treatment options and service provision

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycaemic control, be addressed.

The goal of insulin treatment is to control the amount of insulin in the bloodstream so that glucose levels are normal or near normal. The treatment of diabetes is based on individual needs. This is a process that starts with the very first insulin injection and continues through to eating the right types and amounts of food and starting an exercise programme.

People with type 1 diabetes must have daily injections of insulin to keep the blood sugar level within normal ranges. Other parts of the treatment protocol may include:

- appropriate foods to manage the blood sugar level
- exercise to lower and help the body use blood sugar
- regular blood testing for blood sugar levels
- regular urine testing for ketone levels.

The goal of nutrition intervention is to assist and facilitate individual lifestyle and behaviour changes that will lead to improved metabolic control. This addresses not only glycaemic control but also other aspects such as dyslipidaemia and hypertension.

The hospital healthcare team dietician, general practitioner, physician and diabetic nurse are all on hand to give advice and guidance. It is essential that individuals with diabetes assume an active role on their care. The therapeutic team should agree the treatment plan with the patient and the family where the patient and the family should be involved in the decision-making process.

Specific treatment will be determined by the physician(s) based on:



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- the patient's age, overall health and medical history
- extent of the disease
- the patient's tolerance for specific medications, procedures or therapies
- expectations for the course of the disease
- the patient's opinion or preference.

The objective of any insulin delivery regimen is to simulate the body's normal secretion of insulin in response to dietary intake, exercise levels and the underlying metabolic state, keeping blood glucose levels as close to normal as possible.

Insulin is essential for survival and is the mainstay treatment for diabetes type 1 patients. Many patients experience significant weight gain with adverse effects on blood pressure and cholesterol levels. It is important then to manage cardiovascular risk factors that might develop as a result of intensive treatment. Pancreas transplantation eventually may be recommended for patients who cannot control glucose levels without frequent episodes of severe hypoglycaemia.

Insulin cannot be taken orally because the body's digestive juices destroy it. Injections of insulin under the skin ensure that it is absorbed slowly by the body for a long-lasting effect. The timing and frequency of insulin injections depend on a number of factors, including the type of insulin, amount and type of food eaten, the person's level of physical activity and the preference for and appropriateness to a patient's lifestyle.

With the help of the healthcare team, people with diabetes will maintain control of their blood glucose, blood pressure and other risk factors that may help in developing the complications of diabetes. This will maximise their quality of life and reduce their risk of developing long-term complications.

## Medication

There are a variety of medications, along with insulin formulations, which help people with diabetes achieve better blood glucose control. These drugs are here described with their actions and the role they play in helping people with diabetes attain a healthy blood glucose range.

### Type 1

#### *Insulin*

People with type 1 diabetes are usually totally dependent on daily administration of insulin injections. The majority of people suffering from diabetes have the NIDDM form. However, up to 30% of them may use insulin injections some, or all, of the time to control their condition. There are various types of insulin and schedules that can be used. It is important that people who take insulin understand how insulin works, what factors affect its action and what schedule will work best for them. The type of insulin preparation and the schedule selected for each individual depend on total insulin needs, blood sugar management goals, age and lifestyle.

The four types of insulin are classified by the speed of action. Short-acting insulin has a relatively rapid onset of action and can be given intramuscularly or intravenously. Intermediate-acting insulin is used for longer periods of action. Combinations of neutral protamine Hagedorn (NPH) and regular premixed are also often used.

Two insulin regimens are in common use today for patients with type 1 diabetes, although there may be hybrid regimens in use by specialist centres:

- twice-daily injections of mixed intermediate- or long-acting insulin with regular (soluble) insulin
- multiple daily injections of regular (soluble) insulin at mealtimes (bolus) and injection(s) of intermediate- or long-acting insulin to provide the basal insulin requirement.

#### *The insulin pump*

The insulin pump is a small, battery-operated device that supplies a continuous amount of insulin to the body. The pump is connected to the body by tubing and a single needle. Insulin that is delivered continuously is called the basal dose and that given before meals is called a bolus dose.

#### *Transplantation*

The comments of the American Diabetes Association on pancreas and islet transplantation in patients with type 1 diabetes are that "successful pancreas transplantation has been demonstrated to be efficacious in improving the patient's quality of life, primarily by eliminating the need for exogenous insulin, daily blood glucose measurements and many of the dietary restrictions imposed by the disorder. Transplantation can also eliminate the acute complications commonly experienced by patients with type 1 diabetes."

Pancreas-only transplants require lifelong immunosuppression to prevent rejection of the graft and potential recurrence of the autoimmune

process that might again destroy pancreatic islet cells. Immunosuppressive regimens used in transplant patients have side-effects whose severity restrict their use to patients who have serious complications of diabetes.

In contrast to pancreas transplantation, which has success rates similar to those of other solid organ transplants, islet transplantation for type 1 diabetes is still considered experimental. Only a small percentage of type 1 diabetic patients who receive an islet transplant are off insulin, compared with more than 80% of patients who receive a whole pancreas transplant.

### Type 2 therapies

Sulphonylureas stimulate insulin production in the pancreas and increase insulin sensitivity at the cellular level. Their side-effects include skin rash, jaundice, sensitivity to sunlight and hypoglycaemia.

Metformin increases insulin sensitivity at the cellular level with no effect on the pancreas, hence there is no danger of hypoglycaemia from this drug. Side-effects include gastrointestinal problems, usually nausea, vomiting and diarrhoea, in up to 30% of patients.

α-Glucosidase inhibitors work in the small intestine to slow carbohydrate and delay glucose absorption. Side-effects include nausea, diarrhoea and flatulence.

Thiazolidinediones are oral glucose-lowering drugs specifically designed for type 2 diabetes. They reduce insulin resistance through the activation of peroxisome proliferator-activated receptor-gamma.

## Management guidelines

There are no UK consensus guidelines on the management of people with type 1 diabetes. However, the European Diabetes Policy Group of the International Diabetes Federation published some guidelines in 1998.

The publication *A Desktop Guide to Type 1 (Insulin-dependent) Diabetes Mellitus* can be found at the website: www.staff.ncl.ac.uk/philip.home/t1dgw6b.doc

The aim of these guidelines is to enable a life of normal length and fulfilment for people with diabetes through:

- provision of skills to adapt insulin therapy to lifestyle
- development of understanding to allow coping with new challenges
- control of risk factors for eye, kidney, foot, and arterial damage
- early detection and management of any complications of diabetes

## The burden of disease

The financial costs of IDDM vary enormously depending on whether they include all costs or only healthcare costs, and on whether they include the costs associated with the co-morbidities of diabetes.

The estimated total cost to the NHS of diabetes mellitus (type 1 and 2) was estimated at £1 billion for England and Wales in 1989[9] and consumes at least 5% of health resources.[4]

## Basal insulins

The two existing formulations of insulin used as basal therapy are Ultralente and Neutral Protamine Hagedorn (NPH). NPH accounts for 84% of the current basal insulin prescribed in the UK and is the most relevant comparator to insulin glargine.

The aim of basal insulin is to provide a constant level of insulin between meals, without increasing the risk of hypoglycaemia, particularly at night. The ideal basal insulin has a profile of action that has no pronounced peaks, reproducible glycaemic control and once-daily administration. NPH activity peaks 3–5 hours after administration and has a duration of action of only 14 ± 3 hours and hence has to be injected twice daily.[10]

## Description of new intervention

Insulin glargine (Lantus®) is a long-acting analogue of human insulin. It can be used in basal bolus regimes in patients with type 1 and 2 diabetes, and in patients with type 2 diabetes who require insulin as part of their treatment regime.[11] Insulin glargine is produced by recombinant DNA technology utilising a non-pathogenic laboratory strain of *Escherichia coli* as the production organism.[12]

The action profiles of many basal insulins peak within a few hours of administration, increasing



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the possibility of hypoglycaemic episodes, especially at night, and thereafter wane. Clinical trial data shows a slower, more prolonged absorption rate[13] and a relatively constant concentration–time profile over a 24-hour period with no pronounced peaks compared with NPH human insulin, allowing for once-daily dosing of insulin glargine. Insulin glargine is a clear solution in which no shaking is required before injection. This may result in less intra- and interpatient variability.

## Outcome measures

### Principal goals of treatment

The principle aim of treatment in diabetes is the reduction of mortality and morbidity resulting from increased glycosylated haemoglobin ($HbA_{1c}$) while maintaining a good quality of life. The $HbA_{1c}$ level should ideally be ≤ 7%, but adjusted to accommodate rates of hypoglycaemia acceptable to people living with diabetes. Insulin secretion in non-diabetic people is characterised by continuous basal secretion with peaks immediately after meals and steady release throughout the night. Insulin requirements are at a low during early mornings.

### Glycaemic control

The Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) demonstrated that $HbA_{1c}$ must be reduced to <7% to minimise or prevent the development of microvascular complications.

### Cardiovascular risk factors

CVD is a major complication and the leading cause of premature death among people with diabetes. Adults with diabetes are two to four times more likely to have heart disease or suffer a stroke than people without diabetes. An approximate 1% reduction in all improvements in blood glucose ($HbA_{1c}$), lipids and blood pressure values results in a decreased risk for diabetes complications (Owens D, Professor and Consultant Diabetologist at Llandough Hospital, Cardiff: personal communication, 2002).

# Chapter 3

# Clinical effectiveness

## Methods for reviewing effectiveness

### Search strategies

The search aimed to identify all references relating to the clinical and cost-effectiveness of long-acting insulin analogues (insulin glargine) for diabetes.

### Sources searched

Fourteen electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. A list of databases is provided in Appendix 1.

In addition, the reference lists of relevant articles were checked and 45 health services research related resources were consulted via the Internet. These included health technology assessment organisations, guideline producing bodies, generic research and trials registers and specialist diabetes sites. A list of these additional sources is given in Appendix 2. Finally, citation searches of key papers were undertaken using the Science Citation Index (SCI) citation facility and the reference lists of included studies were checked for additional studies.

### Search terms

A combination of free-text and thesaurus terms was used. Search terms included glargine, glargin, hoe901, hoe 901, lantus, and 160337-95-1. Copies of the search strategies used in the major databases are included in Appendix 3.

### Search restrictions

No date, language, study or publication type restrictions were applied.

### Inclusion and exclusion criteria

The search strategy identified about 900 references. Titles and abstracts of all retrieved papers were screened for relevance to the study question. Most references were either preclinical studies, treatment guidelines or general review articles. All relevant review articles were examined for further references to primary research.

Full copies were obtained of primary research reports (Phase 2, 3 or 4 clinical trials), reviews and abstracts. Aventis supplied us with a list of peer-reviewed articles on glargine primary research. This list was checked to ensure that we had included all those articles cited.

Studies were assessed on the following criteria and studies that met all the criteria were included:

1. Intervention: insulin glargine.
2. Comparator: other long-acting basal insulin.
3. Participants: patients with type 1 diabetes and patients with type 2 diabetes requiring insulin for glycaemic control.
4. Outcome measures: glycaemic control (blood glucose, $HbA_{1c}$). Incidence and severity of hypoglycaemic episodes.
5. Study methodology included at least one of the following:
   (a) systematic review
   (b) randomised controlled trial (RCT)
   (c) economic evaluations
6. Length of study was at least 4 weeks.

### Data extraction strategy

Data extraction was done by one reviewer. Customised data forms were designed to a protocol based on example data extraction sheets.[14]

### Quality assessment strategy

Quality scores for each of the included RCTs were assigned according to the Jadad scale.[15] This scale has some limitations in this context, as most of the trials reviewed were not double-blinded. There are some problems in using a summary score with trials that are not double-blinded. This reduces the possible total Jadad score, thus reducing the discriminatory power of the scale. Nevertheless, quality scales can provide a useful overall assessment when comparing populations of trials. Juni and colleagues[16] suggest that relevant methodological aspects should be identified *a priori* and assessed individually. Following this advice, not only were Jadad scores assessed for the studies here, but also specific information about blinding of those carrying out outcome measures was sought and recorded for each trial.



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# Results of search

## Number of studies

Three structured reviews of primary research on insulin glargine were identified.[17–19] Nineteen references to primary clinical research were identified in the literature search. These references relate to nine clinical trials of type 1 patients and six clinical trials of type 2 patients that appeared to meet the inclusion criteria. Of the 19 references, eight were conference abstracts of trials with type 1 patients and six were conference abstracts of trials with type 2 patients. Four full papers of trials with type 1 patients and two full papers of trials with type 2 patients were published and available in English. Two studies were unpublished abstracts included in the Aventis submission.[20,21]

## Number of studies included

Thirteen studies met the inclusion criteria. All were prospective studies and nine were described as RCTs. None of the trials were double-blinded, but two compared two formulations of insulin glargine with NPH[22,23] using partially blinded designs. Details of the studies are given in *Tables 1* and *2*. Included studies relate to four relevant treatment options.

(1) Type 1 diabetes patients. Two formulations of insulin glargine compared with each other and with NPH.[22,23]
(2) Type 1 diabetes patients. Insulin glargine compared with NPH.[24–29]
(3) Type 2 diabetes patients. Two formulations of insulin glargine compared to each other and with NPH.[30,31]
(4) Type 2 diabetes patients. Insulin glargine compared with NPH.[32,–34]

## Study design

Aspects of study design are summarised in *Tables 3* and *4*. Most trials were reported of either type 1 or type 2 adults with diabetes. One trial was of children with type 1 diabetes.

## Abstract reports

It is not possible to assess from abstracts the quality of studies or the relevance of participants and procedures. Less confidence can be attached to the value of information from these. Therefore, these are summarised separately from full reports. Three of four abstracts[26–28] of studies of type 1 patients reported a regime of NPH twice daily compared with insulin glargine once daily with both groups using premeal insulin. One abstract of a study of type 1 patients[29] reported a regime of NPH once or twice daily compared with insulin glargine once daily, both groups using premeal insulin. One abstract of a study of type 2 patients[34] compared NPH once daily with glargine once daily in patients previously using NPH and who continued to use premeal insulin during the trial. One abstract of a study of type 2 patients[30] did not specify the dosage regime and compared NPH with insulin glargine while maintaining existing oral antidiabetic medication. This trial did not report whether premeal insulin was used. One abstract of a study of type 2 patients[31] compared NPH with insulin glargine in patients previously on oral antidiabetic medication and who stopped this medication during the trial. This trial did not report whether premeal insulin was used.

All abstracts reported a measure of glycaemic control as the primary outcome measure, either fasting blood glucose (FBG), FPG or $HbA_{1c}$. Some studies also reported the incidence and severity of hypoglycaemic episodes.

## Full reports

The four studies[22–25] of type 1 patients recruited patients for whom glycaemic control was effected using a basal-bolus regime. One study of type 2 patients[32] recruited patients who had been using insulin for at least 3 months and one study[33] recruited insulin-naïve patients. Patients in five studies[22–25,32] used NPH either once or twice daily or insulin glargine once daily. Patients in one study[33] used either NPH or insulin glargine once daily. All patients in type 1 studies[22–25] used bolus insulin for postprandial glycaemic control. In five studies[22–25,32] patients randomised to receive NPH had one or two daily injections based on their pre-trial regime. In five studies[22–25,32] the initial dose of insulin glargine was individually determined, based on the pretrial dose of NPH. In one study[33] patients were insulin-naïve. During this trial, individual insulin doses were left to the discretion of the investigator. During each trial, insulin doses were individually titrated and adjusted in an attempt to achieve the target FBG for each person. Two trials[22,23] had titration periods of 3 weeks, followed by a post-titration (treatment) phase of 1 week in which insulin doses remained stable for each individual. Two trials[24,25] had titration periods of one month, followed by 1 weeks[24] and 24 weeks[25] of treatment during which insulin doses remained stable. Two studies[22,23] based titration on a target FBG of 4–7 mmol/l. Two studies[25,33] based titration on target FBG of < 6.7mmol/l. One study[24] based titration on a target FBG of 4.6–6.7 mmol/l. One study[32] based titration on a target FBG of 4.6–6.7 mmol/l.

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**TABLE 1** *Studies included in the review: type 1 patients*

| Study | Diabetes patient group | Countries (number of centres) | Treatment dates (month/year) | Source of report | Comparison | Study type |
|---|---|---|---|---|---|---|
| 32[23,37,38] | Type 1 | Europe (42) | Received for publication May 1999 | Journal article | Insulin glargine [30] vs insulin glargine [80] vs NPH | Open-label RCT with partial blinding |
| 23[24] | Type 1 | Reported in USA (60) | 10/1997–7/1998 | Journal article | Insulin glargine vs NPH | Open-label RCT |
| 37[25] | Type 1 | Reported in USA (49) | Data presented June 1999 | Journal article | Insulin glargine vs NPH | Open-label RCT |
| 30[22] | Type 1 | Reported in USA (–) | Received for publication December 1999 | Journal article | Insulin glargine [30] vs insulin glargine [80] vs NPH | Open-label RCT with partial blinding |
| 170[26,39] | Type 1 | Reported in USA (–) | Published 2001 | Abstract | Insulin glargine vs NPH | Not described |
| 190[27] | Type 1 | Reported in USA (–) | Published 2001 | Abstract | Insulin glargine vs NPH | Not described |
| 253[28] | Type 1 | Reported in USA | Published 1998 | Abstract | Insulin glargine vs NPH | Randomised open-label Phase 2 clinical trial |
| 1065[29] | Type 1 | Reported in England | Published 2000 | Abstract | Insulin glargine vs NPH | Randomised open-label trial |

**TABLE 2** *Studies included in the review: type 2 patients*

| Study | Diabetes patient group | Countries (number of centres) | Treatment dates (month/year) | Source of report | Comparison | Study type |
|---|---|---|---|---|---|---|
| 20[32] | Type 2 not taking oral agents, receiving insulin treatment for ≥ 3 months | Reported in USA (59) | Received for publication May 2000 | Journal article | Insulin glargine vs NPH | Open-label RCT |
| 31[33] | Type 2 insulin-naïve with poor glycaemic control using oral antidiabetic agents | Reported in Finland (–) | Received for publication March 2000 | Journal article | Insulin glargine [30] vs NPH | Open-label RCT |
| 172[34,40] | Type 2 previously treated with once-daily NPH | Reported in USA (–) | Published in 2001 | Abstract | Insulin glargine vs NPH | Randomised study |
| 251[30] | Type 2 with moderate glycaemic control using oral antidiabetic medication | Reported in USA (–) | Published in 1998 | Abstract | Two formulations of insulin glargine compared with each other and with NPH | Not documented |
| 252[31] | Type 2 with suboptimal management on oral antidiabetic medication | Reported in USA (–) | Published in 1998 | Abstract | Insulin glargine [30] vs insulin glargine [80] vs NPH | Not documented |

***TABLE 3*** *Type 1 studies and the outcome measure reported*

| Study | Diabetic patients | Treatment groups (no. randomised) | Study procedure | Outcome measurements reported |
|---|---|---|---|---|
| 32[23,37,38] | Type 1 diabetic patients previously treated for at least 2 months with basal-bolus regime of NPH once or twice daily plus regular human insulin | Insulin glargine [30] (110). Insulin glargine [80] (113). NPH (110) | 3-week dose titration phase. 1-week dose maintenance phase | FPG, FBG, $HbA_{1c}$, fructosamine, mean of a 7-point blood glucose profile, nocturnal blood glucose at 0300 hours, episodes of hypoglycaemia, antibodies to insulin, antibodies to *E. coli* |
| 23[24] | Type 1 diabetic patients 18–80 years old using NPH for ≥ 1 year, lispro for ≥ 3 months. Serum C-peptide level ≤ 9 mg/dl in the presence of blood glucose ≥ 99.0 mg/dl and $HbA_{1c}$ ≤ 12% | Insulin glargine (310). NPH (309) | 1-4 week screening phase followed by 16-week treatment phase | $HbA_{1c}$, FPG, FBG, hypoglycaemia, insulin antibodies, *E. coli* antibodies, ophthalmic examination for changes in diabetic retinopathy, ECG |
| 37[25] | Type 1 diabetic patients 18–80 years old postprandial C-peptide ≤ 0.5 nmol/l for at least 1 year. $HbA_{1c}$ ≤ 12% | Insulin glargine (264). NPH (270) | 1–4 week screening phase followed by 28-week treatment phase | $HbA_{1c}$, FBG, FPG, hypoglycaemia, insulin antibodies, serious adverse events, adverse events |
| 30[22] | Type 1 diabetic patients 18–70 years old. BMI 18–28 $kg/m^2$. $HbA_{1c}$ <10% postprandial serum C-peptide <0.2 pmol/ml. On basal bolus insulin regimen for ≥ 2 months | Insulin glargine [30] (82). Insulin glargine [80] (86). NPH (88) | 4 weeks: 3 weeks adjusting basal insulin dose according to a titration scheme plus 1 week maintenance of basal insulin | FPG, serial overnight plasma glucose, FBG, blood glucose profile, nocturnal blood glucose, stability of fasting glucose, fasting serum insulin, $HbA_{1c}$ |
| 170[26,39] | Type 1 diabetic patients previously treated with multiple daily injections of insulin | Insulin glargine. NPH twice daily | 1-month titration phase. Patients treated for up to 28 weeks | Number reaching target FBG <6.66 mmol/l. Number reaching target $HbA_{1c}$ ≤ 7%. Episodes of symptomatic and severe hypoglycaemia |
| 190[27] | Type 1 with C-peptide <0.5 mmol/l | Insulin glargine (22). NPH (23) | Patients treated for up to 28 weeks | FPG |
| 253[28] | Type 1 diabetic patients | Insulin glargine (9). NPH (5) | 4-week treatment period | FBG, $HbA_{1c}$ |
| 1065[29] | Type 1 diabetic children | Insulin glargine (174). NPH (175) | 6-months | FBG, $HbA_{1c}$, hypoglycaemia – severe, nocturnal and severe nocturnal |

BMI, body mass index.

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***TABLE 4*** *Type 2 studies and the outcome measures reported*

| Study | Diabetic patients | Treatment groups (no. randomised) | Study procedure | Outcome measurements reported |
|---|---|---|---|---|
| 20[32] | Type 2, aged 40–80 years not taking oral agents, previously received basal insulin for ≥ 3 months with or without postprandial insulin | Insulin glargine (259). NPH (259) | 1–4 week screening phase followed by 28-week treatment phase | $HbA_{1c}$, FBG, hypoglycaemia |
| 31[33] | Type 2, insulin-naïve patients with poor glycaemic control using oral antidiabetic agents. 40–80 years old, BMI <40 kg/m$^2$, 7.5% ≥ $HbA_{1c}$ ≥ 12.0%, duration of diabetes ≥ 3 years, previous oral antidiabetic therapy for at least 1 year | Insulin glargine (214). NPH (208) | 4-week screening phase followed by 52-week treatment phase | $HbA_{1c}$, FBG, symptomatic hypoglycaemia (confirmed by blood glucose <2.8 mmol/l), diurnal blood glucose: before and after each of breakfast, lunch, dinner and at bedtime and 3 am, fasting-serum C-peptide (mmol/l), serum triglycerides (mmol/l), serum HDL cholesterol (mmol/l), serum total cholesterol (mmol/l), systolic/diastolic BP (mmHg) |
| 172[34,40] | Type 2, mean age 57.9 years, mean $HbA_{1c}$ 8.4%, mean FBG 9.3 mmol/l | 100 patients in total | Up to 28 weeks treatment | FBG, $HbA_{1c}$, % reaching target FBG <6.66 mmol/l, % reaching target $HbA_{1c}$ <7% or <8%. Hypoglycaemia – confirmed symptomatic and nocturnal |
| 251[30] | Type 2, age 40–80 years, BMI 21–35, $HbA_{1c}$ >7%, currently taking oral antidiabetic medication | Insulin glargine formula 1 (64). Insulin glargine formula 1 (72). NPH (68) | 2-week screening phase. 4-weeks treatment phase | $HbA_{1c}$, symptomatic nocturnal hypoglycaemia |
| 252[31] | Type 2, $HbA_{1c}$ >7%, currently taking oral antidiabetic medication | Insulin glargine [30] (55). Insulin glargine [80] (51). NPH(49) | 4-week study | FPG, $HbA_{1c}$, fructosamine, hypoglycaemia |

HDL, high-density lipoprotein.

One study of type 2 patients recruited insulin-naïve patients for whom oral antidiabetic agents had failed to establish adequate glycaemic control.[33] The other study of type 2 patients had already received insulin treatment for at least 3 months.[32] Neither study included premeal insulin (that is, a basal-bolus regime) during the trial.

## Efficacy measures

All studies used a measure of glycaemic control as the primary outcome measure – FBG, FPG or $HbA_{1c}$. All studies reported a titration period during which doses of insulin were individually titrated in an attempt to achieve a target FBG. The titration period varied over the studies and was a different proportion of the whole reporting period. Therefore, reported data for FBG and FPG cannot be considered to be independent efficacy measures because they were to a greater or lesser extent manipulated by adjustment of insulin doses. All studies also reported the incidence and severity of hypoglycaemic episodes. Various secondary measures were included, principally safety measures such as antibodies to insulin and *E. coli* and recording of adverse events. Changes in dosages of basal insulin between baseline and study end were reported in all full trial reports.

## Characteristics of study populations

Most studies did not report where patients in the trial were recruited from, although most were described as 'multi-centre'. Information that was extracted from the studies is presented in *Tables 1* and *2*. For all studies, the figures available suggest that there are no significant differences between treatment groups in baseline characteristics.

No study reported data on patient compliance.

## Number and type of studies excluded

Two studies were excluded: one study[35] was for a period of 4 days and the other[36] has yet to report data.

## Quality of studies

It is possible to assess the methodological quality of only those trials for which full reports were available.[22–25,32,33] Of these, four[22,25,32,33] scored 2 (out of a possible 3) on the Jadad scale. One[24] scored 3 and one[23] scored 1. It is not possible to double-blind patients to comparisons between NPH and insulin glargine as the former is a cloudy formulation and the latter is clear. Therefore, for efficacy measures done by the patients themselves, blinding is not possible. However, it would have been possible to impose a blinded assessment procedure. None of the studies reported here describe whether clinic assessments of efficacy measures were blinded.

# Results: type 1 studies

All data for both type 1 and 2 studies are presented in *Tables 5–18*.

## Study abstracts

### *Effect on blood glucose*

**FPG**

Three studies[26,28,29] did not report figures for FPG. One study[27] reported non-significant differences between groups in reductions from baseline to end-point FPG.

**FBG**

One study[27] did not report figures for FBG. Three studies[26,28,29] reported significant differences between groups in reductions from baseline to end-point FBG, with insulin glargine groups showing greater reduction in FBG.

**$HbA_{1c}$**

Two studies[26,27] did not report figures for $HbA_{1c}$. Two studies[28,29] reported non-significant differences between groups for reduction in $HbA_{1c}$ from baseline to end-point.

**Episodes of hypoglycaemia**

Two studies[27,28] did not report episodes of hypoglycaemia. One study[29] reported percentages of each group recording symptomatic, nocturnal and severe hypoglycaemia but did not report tests of significance. One study[26] reported that significantly fewer people in the insulin glargine group experienced episodes of symptomatic hypoglycaemia when confirmed by blood glucose of <2.0 mmol/l and also when unconfirmed by blood glucose measures. The same study showed no difference between groups in the percentage of people experiencing severe hypoglycaemia. These data relate to the post-titration phase (up to 28 weeks) and not the entire trial period.

**Abstracts provided in the Aventis submission**

*Information from the Aventis submission was submitted in confidence to the NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## Full reports

Formal meta-analysis of results of the studies was not possible as insufficient raw data were available. Further, the studies described were of different durations and therefore not directly comparable in

***TABLE 5*** *Patient population of type 1 studies*

| Study | Treatment | Mean age (years) | Male (%) | Caucasian (%) | Mean duration of illness (years) | Mean BMI (kg/m$^2$) | Mean baseline $HbA_{1c}$ (%) |
|---|---|---|---|---|---|---|---|
| 32[23,37,38] | Insulin glargine [30] | 35.6 | 56 | N/S | 11 | 24 | 8.09 |
| | Insulin glargine [80] | 37.5 | 66 | N/S | 8 | 24 | 7.96 |
| | NPH | 35.7 | 62 | N/S | 11 | 24 | 7.85 |
| 23[24] | Insulin glargine | 38.9 | 49 | 96 | 19 | 26 | 7.6 |
| | NPH | 39.5 | 52 | 97 | 18 | 26 | 7.7 |
| 37[25] | Insulin glargine | 38.2 | 53 | N/S | 18 | 26 | 7.7 |
| | NPH | 38.9 | 48 | N/S | 17 | 26 | 7.7 |
| 30[22] | Insulin glargine [30] | 37.5 | 51 | 93 | 17 | 24 | 7.8 |
| | Insulin glargine [80] | 37.0 | 51 | 94 | 16 | 24 | 7.9 |
| | NPH | 37.9 | 53 | 94 | 16 | 25 | 8.0 |
| 170[26,39] | Not documented | | | | | | |
| 190[27] | Not documented | | | | | | |
| 253[28] | Insulin glargine | 24.6 | | | 9.8 | | |
| | NPH | 23.8 | | | 12.3 | | |
| 1065[29] | Not documented | | | | | | |

N/S, not stated.

***TABLE 6*** *Patient population of type 2 studies*

| Study | Treatment | Mean age (years) | Male (%) | Caucasian (%) | Mean duration of illness (years) | Mean BMI (kg/m$^2$) | Mean baseline $HbA_{1c}$ (%) |
|---|---|---|---|---|---|---|---|
| 20[32] | Insulin glargine | 59.5 | 58 | 77 | 13 | 31 | 8.6 |
| | NPH | 59.2 | 62 | 78 | 14 | 30 | 8.5 |
| 31[33] | Insulin glargine | 59 | 55 | N/S | 10 | 29 | 9.1 |
| | NPH | 59 | 53 | N/S | 10 | 29 | 8.9 |
| 172[34,40] | Not documented | | | | | | |
| 251[30] | Not documented | | | | | | |
| 252[31] | Not documented | | | | | | |

***TABLE 7*** *Effects on blood glucose measures: fasting plasma glucose (type 1)*

| | Fasting plasma glucose mean change at end-point from baseline (mmol/l) | | |
|---|---|---|---|
| **Study** | **Insulin glargine** | **NPH** | **Between-group difference** |
| 32[23,37,38] | HOE901[30] : –2.22<br>HOE901[90] : –1.61 | 0.01 | HOE901[30] and [80] together vs NPH: $p = 0.0005$ |
| 23[24] | –39.7 | –12.6 | $p = 0.0001$ |
| 37[25] | –1.67 | –0.33 | $p = 0.0145$ |
| 30[22] | Figures not reported | | HOE901[30] and [80] together vs NPH: $p = 0.0001$ |
| 170[26,39] | | Figures not reported | |
| 190[27] | –3.3 | –1.2 | Not significant |
| 253[28] | | Figures not reported | |
| 1065[29] | | Figures not reported | |



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***TABLE 8*** *Effects on blood glucose measures: fasting plasma glucose (type 2)*

| | Fasting plasma glucose mean change at end-point from baseline (mmol/l) | | |
|---|---|---|---|
| **Study** | **Insulin glargine** | **NPH** | **Between-group difference** |
| 20[32] | | Not reported | |
| 31[33] | | Not reported | |
| 172[34,40] | | Not reported | |
| 251[30] | | Not reported | |
| 252[31] | HOE901[30] : –2.8<br>HOE901[90] : –2.6 | –2.3 | Not significant |

***TABLE 9*** *Fasting blood glucose mean change at end-point from baseline (mmol/l) (type 1)*

| Study | Insulin glargine | NPH | Between-group difference |
|---|---|---|---|
| 32[23,37,38] | HOE901[30] : –0.73<br>HOE901[80] : –0.8 | –0.02 | HOE901[30] and [80] together vs NPH: $p = 0.002$ |
| 23[24] | –30.6 | –10.8 | $p = 0.0001$ |
| 37[25] | –1.12 | –0.94 | $p = 0.3546$ |
| 30[22] | HOE901[30] : –1.5<br>HOE901[80] : –1.8 | –0.3 | HOE901[30] and [80] together vs NPH $p < 0.001$ |
| 170[26] | –1.38 | –0.80 | $p = 0.014$ |
| 190[27] | not reported | | |
| 253[28] | Figures not reported | | $p < 0.01$ |
| 1065[29] | –1.29 | –0.61 | $p = 0.0231$ |

***TABLE 10*** *Fasting blood glucose mean change at end-point from baseline (mmol/l) (type 2)*

| Study | Insulin glargine | NPH | Between-group difference |
|---|---|---|---|
| 20[32] | Figures not reported | | Not significant |
| 31[33] | | Not reported | |
| 172[34,40] | –17.1 mg/dl | –20.3 mg/dl | No test reported |
| 251[30] | | Not reported | |
| 252[31] | | Not reported | |

terms of their effects on the indices of glycaemic control. The results of the studies are tabulated separately (*Tables 7, 9, 11, 15, 16*).

Two studies[22,23] specify two formulations of insulin glargine (HOE901[30] and HOE901[80]), but only one[23] gives some results separately for each formulation compared with NPH. All studies[22–25] report patients in the NPH group as receiving injections once or twice daily (based on their pretrial regime), but only one study[23] reports some results separately for insulin glargine versus each NPH regime separately. One study[23] reported 53% on NPH once daily and 47% on NPH twice daily during the trial, but did not report how many in the insulin glargine group had been on once- and twice-daily regimes. One study[24] reported that 72.5% of the insulin glargine group and 74.4% of the NPH group had been on NPH twice daily before the trial. One study[25] reported that 74% of all patients had used NPH twice daily. One trial[22] reported 70.2% of the insulin glargine group and

***TABLE 11*** *$HbA_{1c}$ mean change at end-point from baseline (%) (type 1)*

| Study | Insulin glargine | NPH | Between-group difference |
|---|---|---|---|
| 32[23,37,38] | HOE901[30] : –0.25<br>HOE901[80] : –0.15 | -0.03 | HOE901[30] and [80] together vs NPH: $p = 0.03$<br>HOE901[80] vs NPH: $p = 0.10$<br>HOE901[30] vs NPH: $p = 0.0087$ |
| 23[24] | –0.06 | –0.11 | $p = 0.8409$ |
| 37[25] | –0.16 | –0.21 | $p = 0.4408$ |
| 30[22] | HOE901[30] : –0.4<br>HOE901[80] : –0.4 | –0.4 | Not significant |
| 170[26,39] | Not reported | | |
| 190[27] | Not reported | | |
| 253[28] | –0.4 | –0.2 | Not significant |
| 1065[29] | Figures not reported | | Not significant |

***TABLE 12*** *$HbA_{1c}$ mean change at end-point from baseline (%) (type 2)*

| Study | Insulin glargine | NPH | Between-group difference |
|---|---|---|---|
| 20[32] | Figures not reported | | Not significant |
| 31[33] | Figures not reported | | Not significant |
| 172[34,40] | –0.35 | –0.44 | Not significant |
| 251[30] | –0.8 | –0.8 | Not significant |
| 252[31] | Figures not reported | | Not significant |

70.5% of the NPH group were on NPH twice daily prior to the trial.

It is very important to consider once-daily and more than once daily NPH pretrial regimens separately in comparison with insulin glargine as the two subgroup analyses have different clinical and cost-effectiveness implications. In the absence of the subgroup analyses in all but one study,[23] the interpretation of differences between NPH and insulin glargine results must be treated with caution.

Most studies show some significant difference in primary efficacy measures between the insulin glargine and NPH treatment groups, with insulin glargine demonstrating superior control of FBG and FPG. Three studies,[22,24,25] did not report a superior effect of insulin glargine over NPH in reducing $HbA_{1c}$ levels.

### *Effect on blood glucose*

#### FPG

Between-group comparisons at study end-point demonstrated that for all studies,[22–25] the average end-point FPG for patients treated with insulin glargine was significantly lower than the average end-point FPG for patients treated with NPH (*Table 7*).

#### FBG

Three studies showed significant superiority of insulin glargine over NPH in reducing FBG.[22–24] One study[25] showed no significant difference in the mean reduction of FBG between glargine and NPH at end-point (*Table 9*).

#### $HbA_{1c}$

For three of the four studies,[22,24,25] there were no statistically significant differences in $HbA_{1c}$ at end-point between groups. That is, insulin glargine was reported as not significantly superior to NPH in reducing $HbA_{1c}$. In one study,[23] two different preparations of insulin glargine were used, HOE901[30] and HOE901[80]. HOE901[30] was shown to be superior to NPH in reducing $HbA_{1c}$, whereas HOE901[80] had no significantly different effect on $HbA_{1c}$ than did NPH. Combining the results for HOE901[30] and HOE901[80] showed an overall statistically



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***TABLE 13*** *Recording of hypoglycaemia: type 1 studies*

| Study | Recording of hypoglycaemia |
|---|---|
| 32[23,37,38] | Percentage of patients experiencing at least one episode of hypoglycaemia (<2.8 mmol/l) recorded by patients. Classified as of nocturnal, symptomatic, asymptomatic and severe (requiring assistance). Hypoglycaemia reported as a severe adverse event when it led to coma or car accident |
| 23[24] | Number of episodes. Hypoglycaemic episodes categorised as symptomatic, nocturnal symptomatic and severe. Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the person required assistance from another person and which was accompanied by a blood glucose level of <2.0 mmol/l or associated with prompt recovery after oral carbohydrate, intravenous glucose or glycogen administration. Nocturnal hypoglycaemia was defined as that occurring while the person was asleep during the time between bedtime after the evening injection and before getting up in the morning |
| 37[25] | Percentage of patients experiencing at least one episode of hypoglycaemia. Hypoglycaemia divided into three subsets: all events (with and without confirmation by a blood glucose level of <2.0 mmol/l), severe hypoglycaemia (a symptomatic event requiring the assistance of another individual) and nocturnal hypoglycaemia (occurring while asleep after the bedtime insulin dose and before the morning capillary FBG measurement). Any episode of hypoglycaemia that met the criteria for a serious adverse event (death, life-threatening episode, hospitalisation or medical intervention to prevent permanent impairment) was considered to be a treatment-related adverse event |
| 30[22] | Percentage of patients experiencing at least one episode of hypoglycaemia. Hypoglycaemia was categorised as follows. Symptomatic: symptoms of hypoglycaemia reported by patient that may have been confirmed by a blood glucose level of <2.8 mmol/l. Severe: symptomatic hypoglycaemia in which routine activities were curtailed or assistance was required, may have been confirmed by a blood glucose of <2.8 mmol/l or the prompt recovery of the patient after oral carbohydrate, intravenous glucose or glucagon. Nocturnal: occurring between bedtime basal insulin and FBG determination next morning. Asymptomatic: blood glucose or plasma glucose level <2.8 mmol/l with no symptoms |
| 170[26,39] | Percentage of patients reporting at least one symptomatic event confirmed by blood glucose <2.8 mmol/l. Percentage of patients reporting at least one symptomatic event confirmed by blood glucose <2.0 mmol/l |
| 190[27] | Definition not reported |
| 253[28] | Definition not reported |
| 1065[29] | Hypoglycaemia classified as nocturnal, severe and severe nocturnal |

***TABLE 14*** *Recording of hypoglycaemia: type 2 studies*

| Study | Recording of hypoglycaemia |
|---|---|
| 20[32] | Defined symptomatically and by blood glucose level <2.8 mmol/l. Severe hypoglycaemia defined as an event in which person required assistance and was accompanied by a blood glucose level of <2.0 mmol/l or had prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Nocturnal hypoglycaemia. Defined as occurring when asleep between bedtime after evening injection and before getting up in the morning |
| 31[33] | Hypoglycaemia categorised as symptomatic if clinical symptoms confirmed by blood glucose <2.8 mmol/l or as asymptomatic if an event without symptoms but a blood glucose <2.8 mmol/l. Severe hypoglycaemia defined as an event with symptoms consistent with hypoglycaemia in which person required assistance and was accompanied by a blood glucose level of <2.0 mmol/l or had prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration |
| 172[34,40] | Percentage of patients reporting at least one episode confirmed by blood glucose <50 mg/dl |
| 251[30] | Percentage of patients reporting hypoglycaemia |
| 252[31] | Definition not reported |

significant superiority of insulin glargine over NPH in reducing $HbA_{1c}$ but this difference is not considered to be clinically significant. It is important to bear in mind that the length of this trial was 4 weeks. $HbA_{1c}$ is a measure that reflects average glycaemic control over 6–8 weeks. Therefore, in studies of less than this period, measures of change in $HbA_{1c}$ reflect events occurring prior to the study and cannot be attributed solely to the trial intervention.

**Episodes of hypoglycaemia**

Episodes of hypoglycaemia were classified in all studies as symptomatic, nocturnal and severe. Most studies that reported confirmation of hypoglycaemic episode by a blood glucose measure[22,23,25] used a measure of blood glucose <2.8 mmol/l to confirm hypoglycaemia. However, one study[24] used a measure of blood glucose <2.0 mmol/l to confirm hypoglycaemia. *Table 13* describes classifications and confirmatory blood

***TABLE 15*** *Type 1 studies, hypoglycaemic episodes – entire phase: titration plus treatment phases*

| Study | Treatment | Nocturnal, *n* (%) | Difference | Symptomatic, *n* (%) | Difference | Severe, *n* (%) | Difference |
|---|---|---|---|---|---|---|---|
| 32[23,37,38] | Insulin glargine [30]<br>Insulin glargine [80]<br>NPH | 39 (36)<br>41 (36)<br>61 (56) | $p = 0.0037$[a] | 87 (79)<br>82 (73)<br>87 (79) | $p = 0.5037$ | 7 (6)<br>5 (4)<br>5 (5) | Not significant |
| 23[24] | Insulin glargine<br>NPH | 1114 episodes<br>992 episodes | $p = 0.06$ | 5487 episodes<br>5345 episodes | $p = 0.84$ | 29 episodes<br>20 episodes | $p = 0.44$ |
| 37[25] | Not reported | | | (confirmed by a blood glucose of <2.0 mmol/l), no figures reported | $p = 0.0307$ | Not reported | |
| | | **All hypoglycaemia** | | **Difference** | | | |
| 30[22] | Insulin glargine [30]<br>Insulin glargine [80]<br>NPH | – (97.6)<br>– (100)<br>– (93.2) | | $p = 0.030$ | | | |
| 170[26,39] | Insulin glargine<br>NPH | Not reported | | | | | |
| 190[27] | Not reported | | | | | | |
| 253[28] | Not reported | | | | | | |
| | | **Nocturnal, *n* (%)** | **Difference** | **Severe nocturnal, *n* (%)** | **Difference** | **Severe, *n* (%)** | **Difference** |
| 1065[29b] | Insulin glargine<br>NPH | – (48.3)<br>– (50.9) | Not reported | – (12.6)<br>– (17.7) | Not reported | – (23.0)<br>– (28.6) | Not reported |

[a] This difference may depend of whether patients taking NPH received one or two injections. Insulin glargine seems to have a clear advantage compared with NPH once daily, but the total number of patients with nocturnal hypoglycaemia was very similar when glargine was compared with NPH twice daily.
[b] Abstract does not specify whether data relate to entire phase or treatment phase only.

glucose levels of hypoglycaemia. All studies reported data for the entire trial period, including the titration period, and three studies[23–25] for the treatment period alone. There is some discrepancy between the study results in terms of the difference between the effects of insulin glargine and NPH on number of people reporting at least one hypoglycaemic episode. Three studies[23–25] reported results over the whole trial phase and the post-titration phase for nocturnal and symptomatic hypoglycaemic episodes separately. One 4-week study[22] reported all hypoglycaemia for the whole trial period and not the post-titration phase alone.

**Nocturnal hypoglycaemia**

One study[23] reported significantly fewer episodes of nocturnal hypoglycaemia in the insulin glargine groups together versus NPH over the whole trial, but only for insulin glargine[80] compared with NPH and not for the insulin glargine[30] formulation compared with NPH over the post-titration phase. In this study, there was a clear advantage of insulin glargine over NPH once daily in reducing hypoglycaemia, but the number of patients with nocturnal hypoglycaemia was very similar when insulin glargine was compared with NPH twice daily. One study[25] reported less nocturnal hypoglycaemia in the glargine group compared with NPH for the post-titration phase. One study[24] showed no difference between glargine and NPH in nocturnal hypoglycaemia. One study[22] did not report nocturnal hypoglycaemia separately.

**Symptomatic hypoglycaemia**

One study[25] reported less symptomatic hypoglycaemia in the glargine group compared with NPH for both the whole trial and post-titration phases, where events were confirmed by blood glucose < 2.0 mmol/l, but not during the treatment phase for symptomatic hypoglycaemia



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***TABLE 16*** *Type 1 studies, hypoglycaemic episodes – treatment phase (post-titration phase)*

| Study | Treatment | Nocturnal, *n* (%) | Difference | Symptomatic, *n* (%) | Difference | Severe, *n* (%) | Difference |
|---|---|---|---|---|---|---|---|
| 32[23,37,38] | Insulin glargine [30] | 17(15) | [30] vs NPH: $p = 0.4249$ | 44 (40) | $p = 0.0591$ | 2 (2) | Not significant |
| | Insulin glargine [80] | 9 (8) | [80] vs NPH: $p = 0.0218$ | 32 (28) | | 1 (1) | |
| | NPH | 21 (19) | | 47 (43) | | 1 (1) | |
| 23[24] | Insulin glargine | 774 episodes | $p = 0.65$ | 3719 episodes | $p = 0.60$ | 20 episodes | $p = 0.67$ |
| | NPH | 703 episodes | | 3788 episodes | | 16 episodes | |
| 37[25] | Insulin glargine | – (18.2) | $p = 0.0116$ | – (39.9)[a] | $p = 0.0219$[a] | – (1.9) | $p = 0.0117$ |
| | NPH | – (27.1) | | – (49.2)[b] | $p = 0.0659$[b] | – (5.6) | |
| 30[22] | Insulin glargine [30] | Not reported separately | | | | | |
| | Insulin glargine [80] | | | | | | |
| | NPH | | | | | | |
| 170[26,39] | Insulin glargine | | | – (36.6)[3] | $p = 0.0333$[a] | – (2.6) | Not significant |
| | | | | – (73.3)[4] | $p = 0.0214$[b] | | |
| | NPH | | | – (46.2)[3] | | – (5.1) | |
| | | | | – (81.7)[4] | | | |
| 190[27] | Not reported | | | | | | |
| 253[28] | Not reported | | | | | | |
| 1065[29] | Insulin glargine | – (48.3) | Significance | | | – (23.0) | Significance |
| | NPH | – (50.9) | not stated | | | – (28.6) | not stated |

[a] For events confirmed by a blood glucose of <2.0 mmol/l.
[b] For events not confirmed by a blood glucose of <2.0 mmol/l.

***TABLE 17*** *Type 2 studies, hypoglycaemic episodes – entire phase: titration plus treatment phases*

| Study | Treatment | Nocturnal, *n* (%) | Difference | Symptomatic, *n* (%) | Difference | Severe | Difference |
|---|---|---|---|---|---|---|---|
| 20[32] | Insulin glargine | 81 (35.0) | $p = 0.016$ | 17 (6.6)[a,b] | $p = 0.0553$ | Not reported separately | |
| | NPH | 104 (43.7) | | 27 (10.4)[a,b] | | | |
| 31[33] | Insulin glargine | Not reported separately for entire phase | | | | | |
| | NPH | | | | | | |
| 172[34,40] | Insulin glargine | – (15.4) | $p = 0.0805$ | – (17.3)[c] | $p = 0.002$[c] | Not reported separately | |
| | | | | – (46.2)[d] | $p = 0.049$[d] | | |
| | NPH | – (27.1) | | – (31.3)[c] | | | |
| | | | | – (60.4)[d] | | | |
| | | | | Overall *n* (%) | Difference | | |
| 251[30] | Insulin glargine | No data presented | | – (7.3) | $p < 0.037$ | | |
| | NPH | | | – (19.1) | | | |
| 252[31] | No data presented | | | | | | |

[a] Unclear whether these figures are for entire phase or treatment phase only.
[b] Confirmed by blood glucose value <2.0 mmol/l.
[c] Confirmed by blood glucose value < 2.8 mmol/l.
[d] Unconfirmed by blood glucose value.

***TABLE 18*** *Type 2 studies, hypoglycaemic episodes – treatment phase alone*

| Study | Treatment | Nocturnal, *n* (%) | Difference | Symptomatic, *n* (%) | Difference | Severe | Difference |
|---|---|---|---|---|---|---|---|
| 20[32] | Insulin glargine<br>NPH | 66 (26.5)<br>92 (35.5) | $p = 0.0136$ | See *Table 17* | | Not reported separately | |
| 313[3] | Insulin glargine<br>NPH | Numbers not reported | $p = 0.0001$ | Numbers not reported | $p = 0.04$ | Not reported separately | |
| 172[34,40] | See *Table 17* | | | | | | |
| 251[30] | See *Table 17* | | | | | | |
| 252[31] | No data presented | | | | | | |

unconfirmed by blood glucose. Two studies[23,24] showed no difference between groups in symptomatic hypoglycaemia in either the entire trial period or the post-titration phase. One study[22] did not report symptomatic hypoglycaemia separately.

**Severe hypoglycaemia**
Of three studies reporting severe hypoglycaemia,[23–25] one[25] showed significantly fewer episodes in the glargine group in the post-titration phase. Two studies[23,24] showed no differences between groups in severe hypoglycaemia in either the entire trial period of the post-titration phase.

**Overall hypoglycaemia**
One study[22] reported all hypoglycaemia over the whole trial period. There was significantly less hypoglycaemia in the NPH group than insulin glargine groups. However, the authors stated that this difference is not clinically significant.

**Proportion responding to treatment**
Two studies[22,23] did not report how many people achieved the target FBG at study end. One study[24] reported that 29.6% of people treated with insulin glargine and 16.8% of people using NPH achieved the target FBG at study end, but did not report a test of significance. One study[25] reported 28.7% of people treated with insulin glargine and 24.0% of people using NPH achieved the target FBG at study end, with differences between groups being non-significant.

**Insulin dosage – people whose pretrial regime was NPH once a day**
Two studies[23,24] showed that people taking insulin glargine once a day increased their mean dosage of insulin at trial end by 2 and 1.8 U/day, respectively, compared with baseline. One study[22] showed no change in insulin dose in people taking insulin glargine. For people in the NPH treatment group, two studies[22,24] showed an increased dose of insulin at trial end compared with baseline of 1.8 U/day and an unspecified amount, respectively. One trial[23] showed a decrease of 0.5 U/day at trail end compared with baseline.

**Insulin dosage – people whose pretrial regime was NPH twice a day**
Three studies[22–24] reported that people taking insulin glargine in the trial decreased their mean dose of insulin by 4, 6.2 and between 6 and 7 U/day compared with insulin dose at baseline.

One study[25] did not report basal insulin figures separately for pretrial NPH regimes, but reported that in the trial, insulin glargine patients used 5 U/day less insulin than at baseline and NPH patients used 1.8 U/day more than at baseline.

**Use of regular insulin**
Two studies[23,24] reported no change in the use of regular, premeal insulin. One study[24] did not report regular insulin use. One study[25] showed that patients in the NPH group increased regular insulin use by 1.7 U/day compared with baseline and patients in the glargine group increased regular insulin use by 3.8 U/day compared with baseline.

# Results: type 2 studies

## Study abstracts

### *Effect on blood glucose*

**FPG**
One study[30] did not report FPG. One study[31] reported a non-significant difference between groups in reduction of FPG from baseline to end-point.



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**FBG**
Neither study[30,31] reported FBG.

**$HbA_{1c}$**
Both studies[30,31] reported non-significant differences between groups in reduction of $HbA_{1c}$ from baseline to end-point.

**Episodes of Hypoglycaemia**
One study[30] reported significantly fewer people in the glargine group experiencing at least one episode of symptomatic hypoglycaemia. It is not clear whether these data refer to the entire trial period (4 weeks) or the post-titration phase alone (2 weeks). No other data on hypoglycaemia were presented for either study.[30,31]

## Full reports

Formal meta-analysis of results of the studies was not possible as insufficient raw data were available. Further, the studies described were of different durations and therefore not directly comparable in terms of their effects on the indices of glycaemic control. The results of the studies are tabulated separately (*Tables 8, 10, 12, 17, 18*).

Neither study reported measurement of FPG. One study[32] reported a test of FBG and both reported tests of $HbA_{1c}$.

### *Effect on blood glucose*

**FBG**
One study[32] reported a test of group differences in mean change in FBG as not significant (*Table 10*)

**$HbA_{1c}$**
Both studies[32,33] reported a test of group differences in mean change in $HbA_{1c}$ as not significant (*Table 12*).

**Episodes of hypoglycaemia**
*Table 14* describes classifications and confirmatory blood glucose levels of hypoglycaemia. One study[32] reported data for the entire trial period, including the titration period, and one[33] for the treatment period alone.

**Nocturnal hypoglycaemia**
Both studies[32,33] reported significantly fewer episodes of nocturnal hypoglycaemia in the insulin glargine group over the treatment phase and one[32] reported this significant difference for the whole trial. Only one study[33] compared once-daily NPH with insulin glargine and showed a statistically significant difference, although no figures are reported so it is difficult to interpret the clinical significance of these differences.

**Symptomatic hypoglycaemia**
One[33] study reported less symptomatic hypoglycaemia in the insulin glargine group compared with NPH for the post-titration phase. One study[32] reported no significant difference in symptomatic hypoglycaemia between the groups (although it is not clear whether this was the whole trial phase or the treatment phase alone).

**Severe hypoglycaemia**
Neither trial reported severe hypoglycaemia separately.

**Proportion responding to treatment**
One study[32] reported that 29.6% of people treated with insulin glargine and 27.1% of people using NPH achieved the target FBG at study end, but did not report a statistical significance. One study[33] reported that 7.7% of people treated with insulin glargine and 7.6% of people using NPH achieved the target FBG at study end, a difference that is non-significant.

**Insulin dosage**
One study[32] reported comparisons between pretrial insulin dose and study-end individually titrated doses. For people on pretrial once-daily NPH, both the insulin glargine and NPH treatment groups were reported as using slightly more insulin on average than at baseline, although no data are presented. For people on pretrial more than once-daily NPH, patients treated with insulin glargine used less insulin on average (reduced by 4.4 U/day) and patients treated with NPH used on average about the same at end-point compared with baseline. In one study,[33] insulin-naïve patients were recruited. At study end, average doses of insulin were 21 U/day for those treated with NPH and 23 U/day for those treated with insulin glargine.

# Assessment of effectiveness

## Summary of evidence available and synthesis of information

Currently, there are four full reports of patients with type 1 diabetes[22–25] and two full reports of patients with type 2 diabetes.[32,33] In addition, a number of conference abstracts[26–29] describe results of studies of both type 1 and type 2 patients.[30,31,34] There are, therefore, a limited number of studies on which to draw conclusions about the clinical significance of results.

In studies that reported the proportions of patients on once-daily and more than once-daily

regimens,[22–25] between 70 and 80% of trial participants had been on more than once-daily NPH (in one study,[32] patients were insulin-naïve). These figures contrast with usual clinical experience that shows that, of those patients on a basal-bolus regimen, 70% are on a once-daily regimen of basal insulin (Tesfaye S, Sheffield NHS Teaching Hospitals: personal communication, 2002). Further, most studies did not present data separately for different NPH regimens. Therefore, the clinical relevance of the results of these studies to patients in the usual clinical setting is not clear.

Most studies employed a titration period of variable proportion of the whole. Two studies[22,23] of type 1 diabetes adjusted the insulin dose for 75% of the duration of the trial, one study[24] for 20% of the trial and one study[25] for 13% of the whole trial. The titration procedure is based on adjusting insulin doses to attempt to achieve a target FBG; therefore, FBG cannot be considered to be an independent measure of efficacy. The evidence that is available suggests that in type 1 patients, insulin glargine is significantly more effective in reducing FBG and may be more effective in reducing FPG, but these results are difficult to interpret as FBG is not an independent efficacy measure.

The available evidence does not suggest that insulin glargine is better than NPH in reducing $HbA_{1c}$. The only study[23] that did show insulin glargine to be superior to NPH in reducing $HbA_{1c}$ was a 4-week study, and this difference is not considered to be clinically significant. As $HbA_{1c}$ levels are a reflection of overall glycaemic control in a 6–8-week period, the reduction of $HbA_{1c}$ in this study cannot definitely be attributed solely to the trial intervention.

For patients with type 2 diabetes, there is little evidence about whether insulin glargine is superior to NPH in reducing FBG or FPG and what is available suggests that there is no significant difference. There is evidence that insulin glargine is not significantly superior to NPH in reducing $HbA_{1c}$.

Evidence for the superiority of insulin glargine in controlling hypoglycaemic episodes in type 1 patients is equivocal. One study[24] suggests insulin glargine and NPH to be equally effective in controlling nocturnal hypoglycaemia and two studies[23,25] suggest insulin glargine to be superior in controlling nocturnal hypoglycaemia. However, in one study[23] insulin glargine was shown to control nocturnal hypoglycaemia better only in comparison with a once-daily NPH regime and not for a twice-daily NPH regime. In this study, the number of patients reporting nocturnal hypoglycaemia is very similar when insulin glargine is compared with NPH twice daily. Also in this study, the superiority of insulin glargine over NPH in reducing hypoglycaemia exists only for the HOE901[80] formulation of insulin glargine and not for HOE901[30]. Other studies[22,24,25,] do not report separately data for once-daily and twice-daily NPH regimes and either do not specify the formulation of insulin glargine or do not report results separately, so it is not possible to conclude whether reported differences in nocturnal hypoglycaemia are due to the effects of all insulin glargine formulations versus NPH, the HOE901[80] formulation of glargine versus NPH or the NPH dosing regime.

There is some evidence[23,24] that there is no difference between insulin glargine and NPH in terms of the numbers of people experiencing either symptomatic or severe hypoglycaemia and less convincing evidence[25,26] of fewer people experiencing symptomatic hypoglycaemia when treated with insulin glargine. In one study,[22] significantly fewer people treated with NPH reported any hypoglycaemia, but the authors state that this difference is not clinically significant.

For type 2 patients, the evidence available suggests glargine to be superior to NPH in controlling nocturnal hypoglycaemia. The evidence for the control of symptomatic hypoglycaemia is equivocal, and there is no evidence for the improvements in the occurrence of severe hypoglycaemia.

There are insufficient data presented to comment on the significance of reductions or increases from baseline basal insulin dose compared with end-point basal insulin dose in either type 1 or type 2 studies. Similarly, it is not possible to conclude on the significance of changes in pre-meal insulin use.

## Clinical effect size

Most studies did not present results separately for once-daily and more than once-daily pretrial NPH regimens. Most studies did not report the formulation of insulin glargine used and therefore it cannot be assumed that their results are directly comparable with those studies that did, as these showed some differences between two formulations of insulin glargine compared with NPH. It is not possible to specify the insulin dose



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of insulin glargine required to affect both glycaemic measures and hypoglycaemia because insufficient data are presented to make comparisons between dosages required to achieve clinically significant changes.

### Adverse effects of intervention

The most common treatment-emergent adverse reaction was injection site pain. One study[23] reported transient injection site reactions in 3% of NPH patients, 9% of HOE901[80] patients and 3% of HOE901[30] patients. Another study[24] reported 6.1% of insulin glargine patients and 0.3% of NPH patients experiencing injection site pain, and 15.2% of insulin glargine patients and 10.4% of NPH patients in another study[25] reported tolerable injection site reactions. One study[32] reported mild pain at the injection site as more common with insulin glargine (10.4% versus 7.7%), but that there were no dropouts as a result of this. Another study[22] reported injection site reactions as the most frequently reported adverse event related to study medication (although no data are presented), and these were all mild and none resulted in discontinuation from the study.

### Safety

Antibody titres for insulin glargine, human insulin and *E. coli* were the principal safety measures. Of the studies that reported measures of immunological responses to insulin,[22,23,25,32,33] none reported an increase in insulin antibodies in either treatment group. Of the studies reporting evidence of *E. coli* antibodies,[22–24] no evidence was found of any clinical significance.

## Summary and conclusions of the evidence for and against the intervention

The evidence reviewed in this report indicates that insulin glargine is more effective than NPH in reducing FBG but not in reducing $HbA_{1c}$ in patients with type 1 diabetes. In type 2 patients, there is no evidence that insulin glargine is more effective than NPH in reducing FBG or $HbA_{1c}$ and some evidence that the two insulins are as effective as each other in both FBG and $HbA_{1c}$ control.

The evidence concerning control of nocturnal hypoglycaemia is equivocal and suggests that where insulin glargine is demonstrated to be superior to NPH, it is when compared with once-daily and not twice-daily NPH. There is not enough evidence to conclude that insulin glargine is superior to NPH in controlling either symptomatic or severe hypoglycaemia.

# Chapter 4

# Cost-effectiveness of insulin glargine

## Overview of economic assessment

The aim of this chapter is to assess the cost-effectiveness of insulin glargine in its indicated basal-bolus regime. Our economic analysis includes a systematic review of the cost-effectiveness literature relating to insulin glargine and a review of the economic analysis submitted to NICE by Aventis.

The search of the literature found no direct economic assessment of insulin glargine. The search also revealed no economic assessments of NPH insulin. Therefore, the economic review is based solely on a review of the economic model provided in the Aventis submission.[21]

### Methods

A systematic literature search was undertaken for economic assessments of insulin glargine. Methodological details of this search strategy are presented in Chapter 3 (see section 'Search strategies', p. 9).

In addition to the searches conducted above, searches were conducted in the NHS Economic Evaluations Database (NHS EED) and OHE Health Economic Evaluations Database (OHE HEED) to identify specifically cost-effectiveness literature (Appendix 3). This was supplemented by searches in MEDLINE for economic and quality of life literature relating to diabetes (particularly IDDM), hypoglycaemia and the fear of injections (see Appendix 4 for the methodological search filters used).

### Results of the systematic search for economic studies of insulin glargine

There are no published studies investigating the cost-effectiveness of insulin glargine, or indeed any other insulin analogue. In addition, there are no published studies investigating the cost-effectiveness of NPH insulin, the most likely comparator for insulin glargine. The only available economic evidence relating to insulin glargine is that obtained as part of the confidential submission by the sponsoring body, Aventis.[21]

A preliminary review of the RCT evidence relating to insulin glargine found that insulin glargine and NPH insulin induce a similar effect on glycaemic control and, in particular, $HbA_{1c}$. Therefore, it was not deemed necessary to search the literature for evidence of the relationship between $HbA_{1c}$ and the long-term complications of the disease such as retinopathy and nephropathy.

## Critical appraisal of the economic submission for insulin glargine

A structured pro forma[41] was used in the critical appraisal of the economic submission for insulin glargine. The authors of this assessment reviewed the Aventis submission to NICE[21,42–53] and their findings were part of the version of this report considered by the NICE Appraisal Committee. However, Aventis classified all details of this analysis as confidential and they cannot be reproduced here. The outputs of the Aventis model suggested a level of cost-effectiveness for insulin glargine that historically has been considered acceptable to decision-makers. The results of the Aventis model are not presented here as we are unable to publish sufficient methodological details on the Aventis study to assist the reader in judging the validity of the results.

## Models developed by the assessment team

The assessment team developed two economic models to assess the cost-effectiveness of insulin glargine. No evidence was provided to suggest that type 1 patients should be split into two subgroups depending on their previous therapy. We therefore developed one model for type 1 patients and one for type 2 patients. In both of these models, the comparator is NPH insulin.

## The assessment team's type 1 diabetes model

### Cohort information

One of the main differences between the assessment team's model and the Aventis model is that the assessment team's model used only one patient group. The Aventis model is subdivided



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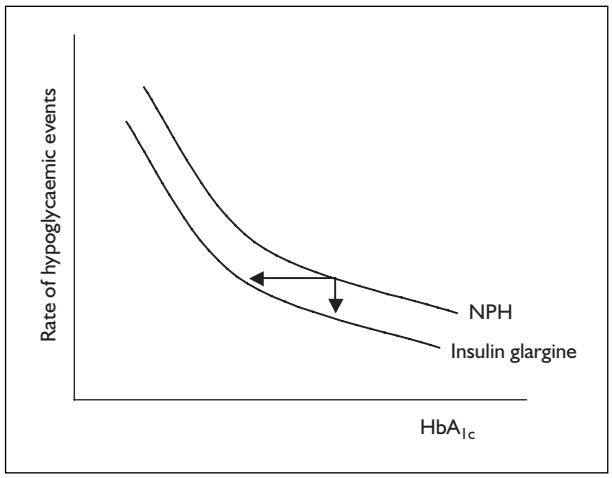


***FIGURE 1*** *Relationship between glycaemic control and hypoglycaemia*

among primary intervention and secondary intervention subgroups, as seen in the DCCT trial.[44] The assessment team's model combines the two and is a weighted average of the two groups.

## Glycaemic control (clinical effectiveness)

The model examined the relationship between glycaemic control and the incidence of hypoglycaemia (*Figure 1*). Two analyses were performed to determine the effect of this relationship on the cost per QALY ratio on insulin glargine.

The central estimate determines the effect on the cost-effectiveness of holding glycaemic control constant and reducing the incidence of hypoglycaemic events. Most of the published trials of insulin glargine in type 1 patients suggest that it induces similar reductions in $HbA_{1c}$[24,25] to NPH but reduces the incidence of hypoglycaemia. Therefore, the central estimate assumes no benefit in $HbA_{1c}$ for patients on insulin glargine. Results from the Ratner trial[25] were used to represent a scenario in which insulin glargine has no additional effect on $HbA_{1c}$ control but significantly reduces the incidence of hypoglycaemic events (42% reduction compared to NPH).

The sensitivity analysis determines the effect on the cost-effectiveness of holding the incidence of hypoglycaemic events constant and improving glycaemic control. Results from the Pieber trial[23] were used to represent a scenario in which insulin glargine does not significantly reduce the incidence of hypoglycaemic events but has additional benefit on $HbA_{1c}$ control (0.14% reduction in $HbA_{1c}$ compared with NPH).

## Clinical outcomes – long-term complications

Since the central estimate assumes that insulin glargine does not achieve better glycaemic control, the incidence of long-term complications is the same in both the insulin glargine and NPH groups.

In the sensitivity analysis, when a difference in $HbA_{1c}$ control is assumed, results from the DCCT trial[44] were used to model the relationship between $HbA_{1c}$ and the incidence of long-term complications. Even though the DCCT trial was a comparison of conventional versus intensive therapy and it is likely that the difference in the incidence in long-term complications between the two treatment groups is not solely attributable to the change in $HbA_{1c}$, this method has been used so that differences between the Aventis model and the assessment team's model can be identified.

## Incidence of hypoglycaemia

It was necessary to calculate the annual number of episodes of symptomatic hypoglycaemia for both insulin glargine and NPH insulin. This was necessary because the literature suggests that there might be a relationship between incidence of symptomatic hypoglycaemia and fear/quality of life. *Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.* The Pampanelli paper[45] was used to estimate the annual number of symptomatic hypoglycaemic events that a patient on NPH insulin would experience. The Ratner trial[25] was used to determine the risk reduction due to insulin glargine. The Ratner trial suggests that the relative risk of a symptomatic hypoglycaemia in type 1 patients is 0.58 (42% reduction in the number of events compared with NPH insulin). This relative risk reduction was applied to the Pampanelli data to estimate the total number of symptomatic hypoglycaemic episodes that an insulin glargine patient would have annually. Therefore, patients receiving insulin glargine and NPH experience 20.6 and 35.6 episodes of symptomatic hypoglycaemia per year, respectively.

It was also necessary to calculate the annual number of episodes of severe hypoglycaemia for both cohorts. However, the assessment team's model calculates the annual rate of severe hypoglycaemia differently from the Aventis model. In the assessment team's model the DCCT trial was used to estimate the annual number of severe hypoglycaemic events for the NPH cohort.[44] In

***TABLE 19*** *Per patients costs over the 9-year period (type 1)*

| Per patient costs | Insulin glargine (£) | NPH (£) |
|---|---|---|
| Total discounted drug cost | 1466–1709 | 735 |
| Costs due to severe hypoglycaemic events | 845 | 1003 |
| Total cost | 2311–2554 | 1738 |

the DCCT trial, the annual rate of severe hypoglycaemia in the conventional treatment group was 0.187 and this value was used to represent the annual rate of severe hypoglycaemia in the NPH cohort. The Ratner trial was then used to estimate the risk reduction due to insulin glargine. The School of Health and Related Research (ScHARR) model differs from the Aventis model in two ways. *Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report*.

The ScHARR model uses the number of severe episodes per 100 patient years. Therefore, in the ScHARR model, patients on insulin glargine and NPH experience an annual rate of severe hypoglycaemia of 0.088 and 0.187, respectively. It is likely that the ScHARR model overestimates the benefit of insulin glargine in avoiding severe hypoglycaemic events. In two of the four type 1 insulin glargine trials, there is no significant difference in the rate of severe hypoglycaemia between insulin glargine and NPH.[23,24] However, this is unlikely to impact significantly the cost per quality-adjusted life-year (QALY) since the cost-effectiveness of insulin glargine is not sensitive to this variable.

## Costs

Costs were identified from an NHS perspective. Only drug costs relating to the basal component of the basal-bolus regime were included. However, this is unlikely to have any effect on the cost-effectiveness ratio. The unit costs associated with the long-term complications were taken from the Aventis submission.[21]

Three types of hypoglycaemia were measured in the trials, symptomatic, nocturnal and severe. It is unlikely that the occurrence of symptomatic or nocturnal hypoglycaemia will incur a cost to the NHS. Severe hypoglycaemia was defined as a hypoglycaemic event in which assistance was required. Therefore, the model only includes a cost for treating severe hypoglycaemia.

Only one estimate relating to the unit cost of a severe hypoglycaemic episode was found in the literature.[48] Nordfelt and Jonsson suggest that the cost of a severe hypoglycaemic event is either €63 or €239 depending on whether the patient becomes unconscious during the event. This implies that the unit cost of a severe hypoglycaemic event is either about £40 or £150, depending on whether the patient becomes unconscious.

ScHARR used data from the CODE-2 study provided in the Aventis submission[21] to determine the cost of a severe hypoglycaemic event.

Another difference between the two models is that the Aventis model does not give a cost in later years to severe hypoglycaemia. In the ScHARR model, the cost of £218 is applied to severe hypoglycaemic events occurring in subsequent years in addition to year 1.

Per patient costs are given in *Table 19*.

## Utilities

The utility weights for the long-term complications of diabetes were taken from the Aventis submission.[21]

Even though there is extensive qualitative literature relating to hypoglycaemia, quality of life during an acute event has not been fully quantified. One possible reason for this is that acute events of hypoglycaemia are of short duration. A study by Nordfelt and Jonsson[48] suggests that patients with severe hypoglycaemia have a lower global quality of life compared to those without (median 0.85 versus median 1.0, $p = 0.0114$). Nordfelt and Jonsson provide no other explanation of how this estimate is derived in the paper. This suggests that patients experiencing a hypoglycaemic event have a 0.15 detriment in utility. This estimate for utility is used in the model to represent the utility associated with a severe hypoglycaemic event. The average length of stay of a non-elective admission for hypoglycaemia taken from the Healthcare Resource Group (HRG) Reference Costs was used



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to represent the number of days that quality of life was affected.[54] The HRG Reference Costs suggest that the average length of stay for a non-elective inpatient episode for hypoglycaemia is 4 days. Therefore, in the model, a severe hypoglycaemic event is associated with a utility detriment of 0.15 for 4 days.

## Quality of life associated with fear of hypoglycaemia

Much of the early literature claims that there is not a significant relationship between hypoglycaemia and long-term quality of life. The DCCT trial measured quality of life outcomes alongside the clinical outcomes when comparing intensive and conventional insulin therapy.[55] In the DCCT trial, the intensive treatment group had three times the number of severe hypoglycaemic events than the conventional treatment group. However, no overall difference in quality of life was seen. This suggests that hypoglycaemic events might not significantly affect long-term quality of life. However, it is possible that the DCCT trial may not have had adequate power to detect an association between hypoglycaemia and quality of life as measured by the diabetes quality-of-life (DQOL) measure.[55]

There is very little conclusive evidence in the literature relating to the relationship between fear of hypoglycaemia utility. The majority of the literature in this area suggests that there is a relationship between fear of hypoglycaemia and general quality of life, but none of these studies linked fear of hypoglycaemia to utility.[56–60]

The only evidence linking hypoglycaemia, fear and utility is that presented in the Aventis submission.[21] However, after reviewing the results provided by Aventis, ScHARR were unsatisfied by the method of analysis. During the course of the appraisal, Aventis revised its estimates of utility gain per hypoglycaemic event avoided and provided more in-depth information relating to the analysis and ScHARR were able to use this in the model. Regression analysis on the dataset suggests that each additional hypoglycaemic event results in a 0.0052 reduction in utility. Therefore, in the ScHARR model, each hypoglycaemic event avoided by insulin glargine results in a 0.0052 increase in utility.

## Mortality

The issue of mortality was addressed in the ScHARR type 1 model. However, in the central estimate, the yearly mortality rate is the same for both cohorts since no difference in $HbA_{1c}$ is assumed. The mortality rate seen in the intensive group of the DCCT trial is used to represent the mortality rate for both insulin glargine and NPH cohorts.[44]

In the sensitivity analysis, when a reduction in $HbA_{1c}$ is assumed, the difference in the mortality rate associated with the intensive and conventional cohorts in the DCCT is used to represent the difference in mortality between insulin glargine and NPH.

## Incremental cost-effectiveness

The ScHARR model suggests that the cost-effectiveness of insulin glargine in type 1 patients ranges from £3496 to £4978 per QALY depending on the method of administration (vial, cartridge or pen).

## Sensitivity analyses

The cost-effectiveness of insulin glargine was truly sensitive to only one variable, the utility gained from reducing fear of hypoglycaemia. However, in the DCCT trial, the intensive cohort had three times the number of hypoglycaemic events as the conventional cohort and no significant difference in quality of life was seen. If the model assumes that the utility gain associated with reduced fear of hypoglycaemia is zero, the cost per QALY increases to between £389,356 and £554,411 depending on the method of administration.

Results of sensitivity analysis are given in *Table 20*.

***TABLE 20*** *Results of sensitivity analysis (type 1).* Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this table

| Variable | Cost per QALY (£) |
|---|---|
| Central estimate | 3,496–4,978 |
| No utility gained from reduced fear | 389,356–554,411 |
| Reduction in $HbA_{1c}$, no reduced hypoglycaemic events | 16,011–23,207 |
| Costs and QALYs discounted at 6% | 4,113–5,857 |
| Costs 6%, QALYs undiscounted | 3,297–4,694 |
| Using Aventis fear/utility assumption | 954–1,358 |

*Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## The ScHARR type 2 diabetes model

This model estimates the cost–utility of insulin glargine in type 2 diabetic patients. The comparator is NPH insulin. The time horizon of the model is 10 years since the rate of diabetic complications is based on data from the 10-year UKPDS trial.

### Glycaemic control (clinical effectiveness)

As with type 1, the model examined the relationship between glycaemic control and the incidence of hypoglycaemia (*Figure 1*). Two analyses were performed to determine the effect of this relationship on the cost per QALY ratio on insulin glargine.

The central estimate determines the effect on the cost-effectiveness of holding glycaemic control constant and reducing the incidence of hypoglycaemic events. All of the published trials of insulin glargine in type 2 patients suggest that insulin glargine and NPH insulin induce similar reductions in $HbA_{1c}$[24,25] but reduce the incidence of hypoglycaemia. Therefore, the central estimate assumes no benefit in $HbA_{1c}$ for patients on insulin glargine. Results from the HOE 4002 trial[2] were used to represent a scenario in which insulin glargine has no additional effect on $HbA_{1c}$ control but significantly reduces the incidence of hypoglycaemic events (18.84% reduction compared with NPH).

The sensitivity analysis determines the effect on the cost-effectiveness of holding the incidence of hypoglycaemic events constant and improving glycaemic control. Results from the Pieber trial[23] were used to represent a scenario in which insulin glargine does not significantly reduce the incidence of hypoglycaemic events but has additional benefit on $HbA_{1c}$ control (0.14% reduction in $HbA_{1c}$ compared with NPH). The Pieber study was used in type II patients owing to a lack of other data. By using the Pieber data, the model assumes that the effect of insulin glargine on $HbA_{1c}$ control is the same in type 1 and type 2 patients.

### Clinical outcomes – long-term complications

Since the central estimates assume that insulin glargine does not achieve better glycaemic control, the incidence of long-term complications is the same in both the insulin glargine and NPH groups.

In the sensitivity analysis, when a difference in $HbA_{1c}$ control is assumed, results from the UKPDS trial were used to model the relationship between $HbA_{1c}$ and the incidence of long-term complications. Even though the UKPDS trial was a comparison of conventional versus intensive therapy and it is likely that the difference in the incidence in long-term complications between the two treatment groups is not solely attributable to the change in $Hba_{1c}$, this method was used so that differences between the Aventis model and the assessment team's model can be identified. The model assumes that the NPH cohort experience the same rate of complications as was seen in UKPDS38 trial.[51] The UKPDS38 trial included older type 2 patients with established diabetes and also suffering from hypertension, which is more likely to reflect the population intended for insulin glargine use. The insulin glargine cohort experience a reduced rate of diabetic complications. For each of the long-term complications examined, the model uses the relative risk reduction seen in the UKPDS33[49] to represent the difference in the risk of experiencing these events for NPH and for glargine.

### Incidence of hypoglycaemia

The clinical trials of insulin glargine suggest that insulin glargine patients experience significantly fewer hypoglycaemic events than patients receiving NPH. The model includes both symptomatic and severe hypoglycaemic events.

Data from the HOE 901/4002 study (Aventis data on file) were used to estimate the annual number of symptomatic hypoglycaemic episodes experienced by patients on insulin glargine and NPH. *Information from the Aventis submission was submitted in confidence to NICE and was used by the assessment team. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report*. This difference in the risk of symptomatic hypoglycaemia between the two treatment groups is used to calculate the utility gained by reducing the fear of hypoglycaemia.

The rate of severe hypoglycaemia in the two treatment groups is used to estimate the amount



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***TABLE 21*** *Per patients costs over the 9-year period (type 2)*

| Per patient costs | Insulin glargine (£) | NPH (£) |
|---|---|---|
| Total discounted drug cost | 2293–2675 | 1150 |
| Costs due to severe hypoglycaemic events | 189 | 194 |
| Total cost | 2482–2864 | 1344 |

of acute utility lost during a hypoglycaemic event. Data from the Diabetes Audit and Research in Tayside Scotland (DARTS) study (data provided in the Aventis submission[21]) are used to estimate the annual rate of severe hypoglycaemic episodes experienced by NPH patients. *Information from the Aventis submission was submitted in confidence to NICE and was used by the assessment team. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report*. The model uses the relative risk from the HOE 901/4002 trial to calculate the reduced rate of severe hypoglycaemia for patients receiving insulin glargine. However, since rates of severe hypoglycaemia are not reported for the HOE 901/4002 trial and neither of the published type 2 trials report results for severe hypoglycaemia, the model uses the relative risk associated with symptomatic hypoglycaemia instead of the relative risk associated with severe hypoglycaemia. By making this assumption, ScHARR are assuming that the risk reduction seen for symptomatic hypoglycaemia also holds for severe hypoglycaemia. *Information from the Aventis submission was submitted in confidence to NICE and was used by the assessment team. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## Costs

Costs were identified from an NHS perspective. Only drug costs relating to the basal component of the basal-bolus regime were included. However, this is unlikely to have any effect on the cost-effectiveness ratio. The unit costs associated with the long-term complications were taken the Aventis submission.[21]

In the ScHARR model, the cost of £218 is applied to severe hypoglycaemic events.

Per patient costs are given in *Table 21*.

## Utilities

The utility weights for the long-term complications of diabetes were taken from the Aventis submission.[21]

The type 2 model also uses the estimate from Nordfelt and Jonsson[48] to represent the utility detriment associated with a severe hypoglycaemic event. This utility detriment of 0.15 is applied for 4 days.

## Quality of life associated with fear of hypoglycaemia

There is very little conclusive evidence in the literature relating to the relationship between fear and hypoglycaemia utility. The majority of the literature in this area suggests that there is a relationship between fear of hypoglycaemia and general quality of life, but none of these studies linked fear of hypoglycaemia to utility.[56–60]

The only evidence linking hypoglycaemia, fear and utility is that presented in the Aventis submission.[21] However, after reviewing the results provided by Aventis, ScHARR were unsatisfied by the method of analysis. During the course of the appraisal, Aventis revised its estimates of utility gain per hypoglycaemic event avoided and provided more in-depth information relating to the analysis and ScHARR were able to use this in the model. Regression analysis on the dataset suggests that each additional hypoglycaemic event results in a 0.0052 reduction in utility. Therefore, in the ScHARR model, each hypoglycaemic event avoided by insulin glargine results in a 0.0052 increase in utility.

## Mortality

The issue of mortality was addressed in this model. However, in the central estimate, the yearly mortality rate is the same for both cohorts since no difference in $HbA_{1c}$ is assumed. The mortality rate seen in the UKPDS33 is used to represent the mortality rate for both insulin glargine and NPH cohorts.[44]

In the sensitivity analysis, when a reduction in $HbA_{1c}$ is assumed, the mortality rate seen in the UKPDS38 is used to represent the mortality rate in the NPH cohort. The percentage reduction in $HbA_{1c}$ that is assumed in the model is used to calculate the reduced rate of mortality in the insulin glargine cohort.

***TABLE 22*** *Results of sensitivity analysis (type 2).* Information from the Aventis submission was submitted in confidence to the NICE. This information was made available to the NICE Appraisals Committee but has been removed from this table

| Variable | Cost per QALY (£) |
|---|---|
| Central estimate | 32,508–43,411 |
| No utility gained from reduced fear | 7,649,327–10,214,864 |
| Reduction in $HbA_{1c}$, no reduced hypoglycaemic events | 71,978–96,192 |
| Costs and QALYs discounted at 6% | 38,657–51,622 |
| Costs 6%, QALYs undiscounted | 30,525–40,763 |
| Using Aventis fear/utility assumption | 6,168–8,237 |

## Incremental cost-effectiveness

The ScHARR model suggests that the cost-effectiveness of insulin glargine in type 2 patients ranges from £32,508 to £43,411 per QALY depending on the method of administration. The reason the cost per QALY is higher than in type 1 is due solely to the utility gained from reducing fear of hypoglycaemia. Only three episodes of symptomatic hypoglycaemia are avoided per person per year owing to insulin glargine.

## Sensitivity analyses

The cost-effectiveness of insulin glargine was truly sensitive to only one variable, the utility gained from reducing fear of hypoglycaemia (*Table 22*). If the model assumes that the utility gain associated with reduced fear of hypoglycaemia is zero, the cost per QALY increases to between £7,649,327 and £10,214,864.

*Information from the Aventis submission was submitted in confidence to NICE. This information was made available to NICE Appraisals Committee but has been removed from this version of the report.*

## Review of Aventis submission on anxiety-related quality of life impact or hypoglycaemia

*Information from the Aventis submission was submitted in confidence to NICE and was used by the assessment team. This information was made available to NICE Appraisals Committee but has been removed from this version of the report.*



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# Chapter 5

# Impact on the NHS

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. The prevalence of insulin-dependent type 1 and type 2 diabetic subjects is estimated to be in the region of 550,000 patients.

## Aventis submission results

The costs presented in *Table 23* were provided in the Aventis submission.

## ScHARR estimates of the impact of insulin glargine on the NHS

This estimate (*Table 24*) uses a prevalence rate of diabetes (for adults) of 2.4% of which 80% are type 2 patients.[4,61] It is assumed that 30% of type 2 patients require insulin; 50% and 15% of type 1 and type 2 patients, respectively, who require insulin use basal-bolus insulin.[21] It is assumed that NPH accounts for 84% of basal-bolus insulin. In the ScHARR estimate, a higher rate of drug uptake is assumed. This estimate assumes that 25, 50 and 100% of NPH patients have switched to insulin glargine in years one, two and three, respectively.

***TABLE 23*** *Impact on the NHS (Aventis estimate of costs, £)*

| | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|
| *Type 1 diabetes* | | | | | |
| Patients on insulin glargine | 919,673 | 3,465,306 | 6,440,695 | 8,379,580 | 10,342,873 |
| Patients otherwise on NPH | 412,654 | 1,554,868 | 2,889,913 | 3,759,882 | 4,640,803 |
| Incremental cost | 507,020 | 1,910,438 | 3,550,783 | 4,619,698 | 5,702,070 |
| *Type 2 diabetes* | | | | | |
| Patients on insulin glargine | 288,416 | 4,387,378 | 9,633,545 | 17,331,818 | 25,606,323 |
| Patients otherwise on NPH | 129,417 | 1,968,695 | 4,322,745 | 7,777,098 | 11,490,017 |
| Incremental cost | 158,998 | 2,418,683 | 5,310,801 | 9,554,720 | 14,116,306 |
| Total incremental cost | 666,018 | 4,329,121 | 8,861,583 | 14,174,418 | 19,818,376 |

***TABLE 24*** *Impact on the NHS (ScHARR estimate of costs, £)*

| | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|
| *Type 1 diabetes* | | | | | |
| Patients on Lantus | 23,026 | 46,219 | 92,768 | 93,100 | 93,762 |
| Cost of Lantus | 5,457,269 | 10,333,768 | 19,567,553 | 18,525,877 | 17,601,623 |
| Cost of NPH | 2,325,671 | 4,403,842 | 8,338,915 | 7,894,994 | 7,501,114 |
| Incremental cost | 3,131,597 | 5,929,926 | 11,228,638 | 10,630,883 | 10,100,509 |
| *Type 2 diabetes* | | | | | |
| Patients on Lantus | 7,747 | 15,550 | 31,212 | 31,323 | 31,546 |
| Cost of Lantus | 2,936,195 | 5,559,917 | 10,528,005 | 9,967,549 | 9,470,269 |
| Cost of NPH | 1,262,796 | 2,391,204 | 4,527,876 | 4,286,835 | 4,072,965 |
| Incremental cost | 1,673,399 | 3,168,713 | 6,000,130 | 5,680,714 | 5,397,303 |
| Total incremental cost | 4,804,996 | 9,098,639 | 17,228,768 | 16,311,597 | 15,497,813 |



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# Chapter 6
# Conclusions

Insulin glargine represents a new technology that reduces the incidence of hypoglycaemic events, in particular nocturnal hypoglycaemic events. The published clinical trials have shown that insulin glargine and NPH insulin achieve similar glycaemic control.

In general, the economic models provided in the Aventis submission were poor. The economic model provided by Aventis was extremely sensitive to one variable, the potential impact on utility gained by reducing the fear of hypoglycaemia. The Aventis models overestimated four-fold the utility benefit that is gained by reducing fear. Therefore, the cost-effectiveness ratios presented in the industry submission are an underestimate owing to this error. The assessment team reassessed the evidence submitted relating to fear and utility and obtained higher cost per QALY ratios; however, there must remain some concern about the validity of methods used to provide important estimates of utility whilst source material remains outside the public domain. The assessment team conclude that insulin glargine is cost-effectiveness in type 1 patients (£3496–4978 per QALY) and borders on cost-effectiveness in type 2 patients (£32,508–43,411 per QALY). This substantial difference in the cost per QALY ratios between type 1 and type 2 diabetes is due solely to the number of hypoglycaemic events that are avoided by insulin glargine.

## Need for further research

The economics of insulin glargine are most affected by the quality of life associated with fear of hypoglycaemia and very little evidence on this has been published. Studies of quality of life need to focus on assessing both the short-term immediate impact of acute episodes of hypoglycaemia including severity and duration and the longer term impact of living with a reduced fear of hypoglycaemia.

The economic impact of the trade-off between control of hypoglycaemia and long-term $HbA_{1c}$ control was investigated by sensitivity analysis. This analysis suggested that, although the economics of insulin glargine were favourable if $HbA_{1c}$ is maintained and hypoglycaemic episodes are reduced, if conversely the incidence of hypoglycaemia is maintained and $HbA_{1c}$ control is improved, the economics of insulin glargine become unfavourable. Although no improvements in long-term glycaemic control were demonstrated in the insulin glargine evidence base, most trials indicate that insulin dosages were titrated up to achieve target FBG levels. It is unclear how far the protocols of the clinical trials are generalisable to how people with diabetes would use insulin glargine in practice. If individuals manage dosing to gain benefits in both $HbA_{1c}$ control and hypoglycaemia events then the economics of insulin glargine would be adversely affected. Further research on the economics of insulin glargine in a realistic practice setting would be beneficial.



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All responsibility for the contents of this report remains with the authors. The views expressed in this report are those of the authors, who are also responsible for any errors.

## About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

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Elaine Weatherley-Jones (Senior Research Fellow) carried out the review of clinical effectiveness. Emma Warren (Operational Research Analyst) and Jim Chilcott (Senior Operational Research Analyst) carried out the review of cost-effectiveness. Catherine Beverley (Systematic Reviews Information Officer) carried out the electronic searches. Emma Warren was also responsible for the report as lead author.

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# Appendix 1

## Electronic bibliographic databases searched

1. *Biological Abstracts*
2. CINAHL
3. Cochrane Controlled Trials Register (CCTR)
4. Cochrane Database of Systematic Reviews (CDSR)
5. Database of Abstracts of Reviews of Effectiveness (DARE)
6. EBM Reviews
7. EMBASE
8. Health Technology Assessment (HTA) Database
9. MEDLINE
10. NHS Economic Evaluations Database (NHS EED)
11. OHE Health Economic Evaluations Database (HEED)
12. PreMedline
13. Science Citation Index
14. Social Sciences Citation Index.



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# Appendix 2

## Other sources consulted

1. Agency for Healthcare Research and Quality (AHRQ)
2. AltaVista
3. Aggressive Research Intelligence Facility (ARIF)
4. Association of British Clinical Diabetologists
5. Association of Diabetes Specialist Nurses
6. Aventis
7. Bandolier
8. British Dietetic Association
9. British Geriatric Society
10. Canadian Coordinating Centre for Health Technology Assessment (CCOHTA)
11. CenterWatch Trials Register
12. Centre for Health Economics, University of York
13. Copernic
14. Current Controlled Trials (CCT)
15. Current Research in Britain (CRiB)
16. Department of Health
17. Diabetes Foundation
18. Diabetes UK
19. eBNF
20. Electronic Medicines Compendium
21. eGuidelines
22. European Agency for the Evaluation of Medicinal Products (EMEA)
23. Food and Drugs Administration (FDA)
24. Health Evidence Bulletins, Wales
25. Heart Disease and Diabetes Research Trust
26. International Network of Agencies for Health Technology Assessment (INAHTA) Clearinghouse
27. Index to Theses
28. Medlineplus Drug Information
29. MeReC
30. Medical Research Council (MRC) Funded Projects Database
31. National Assembly for Wales
32. National Guideline Clearinghouse (NGC)
33. National Research Register (NRR)
34. National Coordinating Centre for Health Technology Assessment (NCCHTA)
35. Organising Medical Networked Information (OMNI)
36. Primary Care Diabetes UK
37. Research Findings Register (ReFeR)
38. Royal College of Physicians
39. ScHARR Library Catalogue
40. Scottish InterCollegiate Guideline Network (SIGN)
41. Trent Working Group on Acute Purchasing
42. Turning Research into Practice (TRIP) Database
43. Wessex Development and Evaluation Committee (DEC) Reports
44. West Midlands Development and Evaluation Services (DES) Reports
45. WHO.



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# Appendix 3

## Search strategies used in the major electronic bibliographic databases

### Biological abstracts

*1985–2001*
*SilverPlatter WebSPIRS*
*Search undertaken January 2002*

#1 glargin*
#2 lantus
#3 hoe901
#4 hoe 901
#5 160337-95-1
#6 #1 or #2 or #3 or #4 or #5

### CDSR and CCTR

*2001 Issue 4*
*The Cochrane Library, Update Software (Internet version)*
*Search undertaken January 2002*

(glargin* or lantus or hoe901 or hoe 901)

### CINAHL

*1982–2001*
*Ovid Biomed*
*Search undertaken January 2002*

1 glargin$.af
2 lantus.af
3 hoe 901.af
4 hoe901.af
5 160337-95-1.rn
6 or/1-5

### CRD Databases (NHS DARE, EED, HTA)

*CRD website – complete databases*
*Search undertaken January 2002*

(glargin or glargine or lantus or hoe901 or hoe 901)/All fields

### EMBASE

*1980–2001*
*SilverPlatter WebSPIRS*
*Search undertaken January 2002*

#1 glargin*
#2 'insulin glargine' / all subheadings
#3 hoe901
#4 hoe 901
#5 lantus
#6 160337-95-1 in rn
#7 #1 or #2 or #3 or #4 or #5 or #6

### HEED (Office of Health Economics Health Economic Evaluation Database)

*CD ROM version*
*Search undertaken January 2002*

#### Search terms

- glargin or glargine or lantus or hoe901 or hoe 901

#### Fields searched

- abstract
- all data
- article title
- book title
- keywords
- technology assessed

### MEDLINE

*1966–2001*
*Ovid Biomed*
*Search undertaken January 2002*

1 glargin$.af
2 lantus.af
3 hoe 901.af
4 hoe901.af
5 160337-95-1.rn
6 or/1-5



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## Science and Social Sciences Citation Index

*1981–2001*
*Web of Science*
*Search undertaken January 2002*

Topic=glargin* or lantus or hoe901 or hoe 901; DocType=All document types; Languages=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years

# Appendix 4

# Economic evaluations and quality of life methodological search filters used in MEDLINE (Ovid) 1966–February 2002

## Economic evaluations

1 economics/
2 exp "costs and cost analysis"/
3 economic value of life/
4 exp economics, hospital/
5 exp economics, medical/
6 economics, nursing/
7 economics, pharmaceutical/
8 exp models, economic/
9 exp "fees and charges"/
10 exp budgets/
11 ec.fs
12 (cost or costs or costed or costly or costing$).tw
13 (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14 or/1-13

## Quality of life

1 exp quality of life/
2 quality of life.tw
3 life quality.tw
4 hql.tw
5 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
6 qol.tw
7 (euroqol or eq5d or eq 5d).tw
8 qaly$.tw
9 quality adjusted life year$.tw
10 hye$.tw
11 health$ year$ equivalent$.tw
12 health utilit$.tw
13 hui.tw
14 quality of wellbeing$.tw
15 quality of well being.tw
16 qwb.tw
17 (qald$ or qale$ or qtime$).tw
18 or/1-17



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# Appendix 5

## Letter asking for more information – sent to Aventis 19 April 2002

*Information from the Aventis submission was submitted in confidence to NICE. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*



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# Appendix 6

## Response to questions from ScHARR/NICE – received from Aventis 25 April 2002

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# Appendix 7

## Further response to questions from ScHARR/NICE – received from Aventis on 29 April 2002

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# Appendix 8

## Update on Appendix 6 – received from Aventis on 3 May 2002

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## Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

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