NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Continuous subcutaneous insulin infusion for the treatment of diabetes

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Diabetes mellitus (DM) is a chronic metabolic disorder caused by insufficient activity of the hormone insulin, due to either a lack of the hormone or resistance to its action. Insulin is produced by the beta cells of the pancreas in response to rising blood glucose levels and mainly regulates the metabolism of carbohydrates, as well as proteins and fats. There are two types of diabetes mellitus. Type 1 diabetes mellitus (T1DM) is caused by the destruction of insulin-producing cells, leading to an absolute lack of the hormone. Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance and can be related to a person being overweight. In T2DM, the pancreas initially responds by increasing insulin production, but over time this excess production cannot be maintained, leading to a relative lack of insulin. Both types of diabetes mellitus are characterised by hyperglycaemia – an elevation of blood glucose levels above normal.

The onset of T1DM usually occurs in children and young adults, with an estimated prevalence in the UK in 2005 of 0.42% (representing 251,000 people). The incidence is increasing, with the greatest increase in children younger than 5 years. T2DM occurs in adults and usually begins after the age of 45 years. Risk factors for T2DM are obesity, age and ethnicity. The current prevalence in England is estimated to be 4.3%. The incidence is rising and expected to rise further, owing to an ageing population and increasing prevalence of obesity.

Diabetes mellitus can cause short- and long-term problems. Short-term problems are acute metabolic emergencies that can be life-threatening, such as diabetic ketoacidosis (DKA) which is a consequence of hyperglycaemia, and hypoglycaemia caused by treatment. Severe hypoglycaemia is defined by the need for assistance from another person for recovery. However, milder hypoglycaemia can be corrected by the diabetic person themselves through an intake of carbohydrates. Long-term complications of diabetes mellitus are caused by damage to small (microangiopathy) and large (macroangiopathy) blood vessels as a consequence of chronically elevated blood glucose levels. This can lead to retinopathy and blindness, nephropathy and renal failure, ischaemic heart disease and myocardial infarctions, strokes and damage to nerves and arteries in the limbs leading to chronic ulcers and often necessitating limb amputations.

1.2 Current management

T1DM requires life-long treatment with insulin. T2DM is initially managed by diet and weight loss. If this is insufficient, oral glucose-lowering drugs are added. Over time, most people will need insulin to control their blood sugar levels.

There are various types of insulin, grouped by the duration of action.

- Soluble short-acting insulins have a rapid onset of action starting within 1 hour of administration, have a peak between 2 to 4 hours, and have some effect for approximately 8 hours. Short-acting analogue insulins

(aspart, lispro, glulisine) have a faster onset and shorter duration of action than soluble insulins. Inhaled insulin, a dry powder, has a faster onset of action than soluble insulin but a similar duration of action

- The duration of action of insulin can be modified by combining it with other substances such as protamine or zinc. Intermediate-acting insulins (neutral protamine Hagedorn [NPH] or isophane) start working in 1 to 2 hours, peak between 6 and 10 hours and have some effect for 16–18 hours.

- Long-acting insulin analogues (glargine and detemir) have a longer and steady (peak-less) duration of action. Analogue insulins are genetically engineered so that they are similar, but not identical, to human insulins.

All types of insulin can be combined in treatment regimens of varying intensity, depending on the degree to which normality of blood glucose levels is sought. Achieving good control of blood glucose through an intensive regimen reduces the risk of complications. Conventional insulin treatment is a twice-daily combination of a short-acting and intermediate-acting insulin. Intensive insulin therapy consists of one or two injections of an intermediate-acting or long-acting insulin that acts as the basal insulin supply together with boluses of short-acting insulin at meal times. The ‘basal-bolus’ regimens are also called multiple-dose insulin (MDI) and are used with blood glucose monitoring, adjustment of insulin dose and attention to diet. Intensive insulin regimens attempt to reproduce the normal secretion of insulin by the pancreas. However, exogenously administered insulin lacks the feedback mechanism that the pancreas uses to regulate insulin secretion, whereby insulin production decreases as blood glucose levels fall.

Insulin requirements change depending on food intake, exercise or intercurrent illness. Therefore, people taking insulin need to check their blood glucose levels regularly by using a monitor (glucometer). Regular measurements enable short-term control of blood glucose levels by adjusting the insulin dose. Long-term monitoring of control is achieved by measuring

glycosylated haemoglobin (HbA_{1c}) levels, which give average blood glucose levels over the preceding 3 months. Good control is indicated by a value of less than 7.5% (normal range for people who do not have diabetes is 4.5–6.1%).

A major acute side effect of the use of insulin is hypoglycaemia. Mild hypoglycaemia can be corrected by oral intake of sugars. Severe hypoglycaemia needs the assistance of another person to correct the hypoglycaemia. The early symptoms are hunger, sweating, tremor, palpitations and headache. However, in some people these early symptoms are absent – which is called hypoglycaemic unawareness – putting them at an increased risk of severe hypoglycaemia and its complications. Hypoglycaemia can also cause convulsions, coma and death. In children, especially those younger than 5 years, hypoglycaemia causes long-term cognitive impairments which are correlated with the frequency and severity of hypoglycaemia. The occurrence of hypoglycaemia is associated with fear of recurrence, which can decrease quality of life and hinder adherence to treatment and therefore the achievement of good glycaemic control. This is because people often regard hypoglycaemic episodes as a more important problem than long-term complications.

2 The technologies

Table 1 Summary description of technologies

Pump	Manufacturer	Cost
Animas IR1200	Animas Corp., Johnson & Johnsons	£2600
Paradigm real-Time MMT-522	Medtronic	£2750
Paradigm real-Time MMT-722	Medtronic	£2750
Accu-Check Spirit	Roche Diagnostics Ltd	£2375
Deltec Cozmo	Smiths Medical Intl.	£2750
Starlet	Starbridge Systems Ltd	Not available

Continuous subcutaneous insulin infusion (CSII) makes use of an external pump that continuously delivers short-acting insulin by means of a subcutaneously placed cannula. The pump can be programmed to deliver a basal rate of insulin throughout the day, with higher infusion rates at meal times, and also to deliver different basal rates of insulin at different times of the day and night. The cannula needs repositioning every 3 days. CSII avoids multiple daily injections and also decreases the fluctuations in insulin levels associated with the use of longer-acting insulins. It can also allow a greater flexibility in lifestyle, and a reduced fear of severe hypoglycaemia, which improve quality of life.

The models of available pumps and their costs are provided in table 1. The pumps usually have a 4-year warranty and in some cases this can be extended by 2 years at an additional cost. However, it is expected that people would usually prefer a new pump. CSII also incurs costs for: batteries, reservoirs, infusion sets, insulin, lancets, test strips and glucometers for monitoring. There is also a one-off cost for patient education when starting treatment with a pump, and additional costs for continued medical support during the time that the person is learning to become self-sufficient with managing their diabetes mellitus.

Currently, NICE guidance (TA 57) recommends CSII as an option for people with T1DM where MDI therapy (including, where appropriate, the use of glargine) has failed, and where the user has the competence and commitment to use CSII therapy effectively. MDI therapy is deemed to have failed when it has been impossible to maintain HbA_{1c} levels at 7.5% or below (6.5% in the presence of microalbuminuria or other risk factors for cardiovascular disease that are features of the metabolic syndrome) without severe hypoglycaemia occurring. In TA 57, CSII is not recommended as a therapy for T2DM. At the time of publication of TA 57, NICE expected that 1–2% of people with T1DM would be eligible for pump therapy.

A recent report by the Insulin Pumps Working Group noted that the UK had a substantially lower use of insulin pumps in people with T1DM (approximately

1%) than countries of comparable economic standing and level of healthcare provision (10–20%). The group felt that the expectation that 1–2% of people with T1DM would be capable of benefiting from CSII therapy was misleading. The group sought clarifications of the term 'failure of MDI' and suggested possible indications in addition to those considered by NICE, including quality of life issues, use in children, use during pregnancy, and use in people with T2DM, hypoglycaemic unawareness and extreme insulin sensitivity.

3 The evidence

3.1 Clinical effectiveness

3.1.1 Joint manufacturers' submission

[redacted]

3.1.2 Assessment report

Summary of clinical-effectiveness results from TA 57

The assessment report for TA 57 identified 20 studies that compared CSII to MDI. Eight were parallel randomised controlled trials (RCTs), nine were randomised crossover studies and three were non-random crossover studies.

Fourteen studies were in adults with T1DM. In two of these studies, the analogue insulin lispro was used for MDI therapy. There was a consistent improvement of approximately 0.6% in HbA_{1c} levels in the CSII group compared with the MDI group. In short-term studies, the insulin dose being administered in the CSII group was lower than in the MDI group by approximately 12 units (20–25%); however, there was little difference in long-term studies. There were no significant differences in the frequency of hypoglycaemic episodes between the CSII and MDI groups, although there was a trend towards lower rates of hypoglycaemia in the CSII group compared with the MDI group; however these differences were not statistically significant. Observational studies found greater reductions in the frequency of severe hypoglycaemia on CSII. There was little evidence on the effects of CSII and MDI therapy on quality of life.

Four studies were in pregnant women with T1DM and T2DM. There were no significant differences between CSII and MDI therapy in terms of HbA_{1c} levels, insulin dose or adverse effects. Adverse pregnancy outcomes occurred infrequently in both groups in all studies, but infant mortality was significantly lower in the CSII group in one study.

Two studies were in adolescents (younger than 20 years) with T1DM. One study found a significant difference in HbA_{1c} levels and insulin dose being administered in favour of CSII, whereas the other did not. Adverse effects were infrequent in both groups in both studies. No studies conducted in children were included in the review of effectiveness.

Six studies (one parallel RCT and five randomised crossover studies) compared the use of rapid-acting analogues (lispro and aspart) with soluble insulin in CSII. The use of analogue insulin lead to a significant decrease in HbA_{1c} levels (0.26%) compared with soluble insulin. There was no difference in the insulin dose being administered and there was no significant difference in the rate of severe hypoglycaemia or other adverse events between the groups.

Update of clinical effectiveness evidence – comparators

To define the most suitable comparator, the Assessment Group carried out a brief search to update the evidence that has emerged since the NICE appraisal of glargine (TA 53) in 2002, comparing long-acting analogue insulins with NPH and ultralente. From the new evidence and the guidance issued in TA 53, the Assessment Group concluded that, in T1DM, analogue-based MDI is more efficacious than NPH-based MDI. Therefore, in T1DM, analogue-based MDI was used as comparator. For T2DM, a Cochrane review from 2007 concluded that there was no benefit of long-acting analogues over NPH. Taking TA 53 into account, which limited the use of glargine in T2DM, the Assessment Group concluded that, in T2DM, the advantage of long-acting analogues over NPH was not proven and both remained valid comparators for CSII in this appraisal.

The Assessment Group conducted a systematic review of new evidence since 2002 and the results are summarised as follows.

CSII versus 'best' analogue MDI

The Assessment Group found four RCTs in T1DM and four RCTs in T2DM that compared CSII with analogue MDI. One RCT conducted in children and adolescents with T1DM showed a significantly lower HbA_{1c} level with CSII than with analogue-based MDI. For adults with T1DM, no difference between CSII and MDI was found. For T2DM, there was little evidence of CSII being better than analogue-based MDI in terms of HbA_{1c} reduction.

A statistically significant reduction in the frequency of hypoglycaemia with CSII compared with MDI was found in only one study in children and adolescents with T1DM. The other studies had too few hypoglycaemic episodes to comment or showed no difference. There was no evidence of a significant difference in insulin dose being administered between the two groups. Many of these studies were of brief duration and the improvement in glycaemic control as evidenced by HbA_{1c} levels cannot be assumed to persist in the longer term.

CSII versus older NPH-based MDI

The Assessment Group reviewed the evidence that has emerged since the original appraisal for CSII (TA 57) versus NPH-based MDI in T1DM. Of the eight studies identified most were small and showed no, or not statistically significant, differences. Only one study showed a statistically significant difference in glycaemic control with an HbA_{1c} decrease of 0.84% favouring CSII over NPH-based MDI.

CSII in pregnancy

A review of the new evidence in pregnancy produced no new RCTs and six new observational studies. All studies were in women with T1DM. The Assessment Group concluded that CSII achieves similar glycaemic control to MDI regimens in pregnant women with T1DM and maternal and foetal outcomes are similar.

Observational studies

The Assessment Group summarised the results of the observational studies cautioning about the risk of bias. However, it has been noted that reduction in hypoglycaemia was greater in observational studies than in RCTs because observational studies possibly selectively recruit people with greater problems with hypoglycaemia. As such, people are more likely to be considered candidates for CSII in routine care; therefore, the outcomes of observational studies may be a better guide to expected outcomes in routine care. Observational studies also provide longer term evidence on outcomes such as discontinuation rates and side effects as well as the benefits that result from people becoming more adept at pump use. A total of 48 observational studies were identified. Of the 22 studies that reported continuation rates, at 1 to 5 years these ranged from 74–100%, showing evidence of patient satisfaction.

Glycaemic control

A total of 46 observational studies reported before and after HbA_{1c} levels. Of these, all 18 studies in the adults/mixed age group showed a significant decrease in HbA_{1c} levels (ranging from 0.2–1.4%) with CSII compared with MDI. Of the 23 studies carried out in the children/adolescent age group, three

showed an increase in HbA_{1c} levels after starting the pump; however, in two of these studies the increase was not statistically significant, and the third study did not report whether the HbA_{1c} increase of 0.6% was statistically significant. In the other 20 studies there was a decrease in HbA_{1c} levels (ranging from 0.2–1.2%) with the difference reaching statistical significance in 13 studies. In five studies in young children, the decrease ranged from 0.2–1.6%, with the change being statistically significant in four of these studies.

Hypoglycaemia

Twenty-six observational studies compared the rate of severe hypoglycaemic episodes in people receiving CSII and MDI. Of the 10 studies in the adult/mixed age groups, eight reported significant decreases in the rate of severe hypoglycaemic episodes with CSII. The rate ratios ranged from 0.07 to 0.4. In remaining two studies there were no episodes before or after commencing pump use. Of the 11 studies in children and adolescents, one had no hypoglycaemic episodes and the other ten reported decreases in their frequency with CSII, with rate ratios ranging from 0.12 to 0.80. In four of these studies the reduction was significant, three did not report significance and three did not show a significant decrease. In the five studies in young children the rate ratios ranged from 0 to 0.81, with the difference being significant in three.

In summary, observational studies showed a decrease in HbA_{1c} levels greater than that reported in RCTs and a considerable reduction in the rate of severe hypoglycaemic episodes in people receiving CSII. There was no increase in the incidence of DKA, some minor weight gain and overall a reduction in daily insulin dose. Of the 21 studies reporting before and after insulin doses, 16 studies showed a decrease in insulin being administered with CSII therapy – this decrease was significant in nine studies, not significant in three studies and of unknown significance (not reported) in four studies. Only five studies reported an increase in insulin dose being administered with CSII; of these, only one increase was significant and another study reported a significant increase in one subgroup.

Other evidence

In addition to the trial evidence above, the Assessment Group noted the results of meta-analyses. These showed that treatment with CSII gave lower HbA_{1c} levels by an average of 0.5% compared with MDI therapy, and when analogue insulins were used in CSII there was a further 0.2% improvement. The benefit of CSII was greater in people with high baseline HbA_{1c} levels and variability of blood glucose. In a before and after study of people who were particularly affected by hypoglycaemia and who switched to CSII therapy after intensive MDI therapy had failed, HbA_{1c} levels were reduced by 1.4%. The Assessment Group also noted that the meta-analysis that formed the basis of the clinical-effectiveness section in the manufacturers' submission showed a greater reduction in HbA_{1c} levels in before-after studies [redacted] compared with RCTs [redacted] Data from the Insulin Pump Clinical Database were also available to the Assessment Group. This database consists of data pooled by a group of centres with considerable experience in the use of insulin pumps in adults and children. These data showed that people receiving CSII therapy had a mean reduction in their HbA_{1c} levels of 0.9%, with a mean HbA_{1c} level of 9.1%. There was also evidence that the initial decrease in HbA_{1c} levels observed after starting CSII therapy may not be sustained. Conversely, brief studies may not capture the full benefit of CSII therapy because people may develop expertise when using the pump over longer periods of time.

3.2 Cost effectiveness

3.2.1 Assessment Group's systematic review

A systematic review of the cost-effectiveness literature for insulin pumps conducted by the Assessment Group found 11 publications. Except for one study, which developed a relatively simple Markov model, all other publications used the CORE (Centre for Outcomes Research) model (although for two publications this is not made explicit but implied). Three studies that were performed in the UK and took the health service perspective resulted in incremental cost-effectiveness ratios (ICERs) for CSII compared with MDI of £11,500, £26,300 and £32,800 per quality-adjusted life year

(QALY) gained. In the cost-effectiveness studies, the commonest assumed baseline improvement in HbA_{1c} levels with CSII therapy compared with MDI was 1.2%. The results of the sensitivity analysis showed that the results were sensitive to improvement in glycaemic control, as measured by the decrease in HbA_{1c} levels and the effect of CSII on the incidence of severe hypoglycaemic episodes.

Both the manufacturers' submission and the Assessment Group's cost-effectiveness modelling were based on the CORE model.

3.2.2 The CORE model

The CORE model is an internet-based interactive computer model that is available under licence from the developers. It is designed as a policy analysis tool to determine long-term clinical and health economic outcomes in people with T1DM and T2DM. The user interface allows definition of the cohort characteristics, setting of treatment definitions and country-specific treatment pathways, input of details of cost and clinical data, specification of the type of analysis to be performed, selection of the appropriate risk engine to be used and setting of preferences for the presentation of results. The risk engine allows the model to predict the probabilities of the occurrence of the various complications in the sub-models. Risk engines are based on large epidemiological trials (UKPDS, Framingham and DCCT) and use regression models to calculate the risk of complications based on patient characteristics.

The cohort is defined in terms of patient demographics (age, gender, ethnic group and duration of diabetes), baseline risk factors (HbA_{1c}, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, body mass index, number of cigarettes smoked per day and alcohol consumption) and baseline existing complications (cardiovascular [myocardial infarction, angina, peripheral vascular disease, stroke, congestive heart failure, atrial fibrillation and left ventricular hypertrophy], renal [microalbuminuria, gross proteinuria and end-stage renal disease], retinopathy [background or proliferative and severe vision loss], macular oedema, cataract, foot ulcer [uninfected or infected,

gangrene, healed ulcer and amputation] and neuropathy). Risk factors are updated with each cycle of the model to simulate natural progression of the disease.

The CORE model uses a number of databases. The clinical database consists of medical and epidemiological data that are used to calculate clinical outcomes. The clinical database is a set of probabilities and risk adjustment factors for disease progression and occurrence of acute events and complications based on the patient characteristics defined above. The treatment database consists of treatment pathways, treatment effects and change in patient characteristics as a consequence of treatment. It also includes the costs associated with treatment (medication, monitoring, investigations and consultations). The economics database includes the direct costs, indirect costs (based on the human capital approach), discount rates and quality of life data.

The CORE model consists of 15 sub-models, each of which simulates a complication associated with diabetes mellitus. Each sub-model is a Markov model using time, state, time-in-state and diabetes type-dependent probabilities to simulate the progress of patients. The sub-models are: angina, cataract, congestive heart failure, foot ulcer and amputation, hypoglycaemia, ketoacidosis, lactic acidosis, macular oedema, myocardial infarction, nephropathy, neuropathy, peripheral vascular disease, retinopathy, stroke and non-specific mortality. For T2DM there is also a treatment sequence sub-model to simulate changes in treatment over time. The model uses tracker variables to allow interaction between sub-models such that progression of complications can influence transition probabilities of other complications where such a link has been clinically established. First- and second-order Monte Carlo simulations with or without distributions on input parameters and non-parametric bootstrap methods are used to evaluate uncertainty.

The CORE model was validated against 11 cohorts from published trials. It was found to be a good predictor of outcomes observed in the cohorts. The Assessment Group considered it a highly developed and well-tested model. It

appeared to overestimate the death rate in people with T1DM, especially as the time horizon increases. This is possibly due to overestimation of the macrovascular complications by the model. The model also assumes that improvements in HbA_{1c} levels that are associated with novel treatments are maintained over time. Given the population characteristics of clinical sources used in the model it is also doubtful whether the model is applicable to the paediatric and adolescent population with T1DM.

3.2.3 Manufacturers' cost-effectiveness analysis

The patient cohort characteristics were based on a UK database of 3000 adults with T1DM followed-up over a period of 9 years. The average age was 37.8 years. Three scenarios for the effect of CSII on HbA_{1c} levels were considered.

From the unpublished confidential meta-analysis that formed the basis of the submission's clinical-effectiveness data, a decrease of [redacted] in HbA_{1c} levels was used in the 'trial-based' analysis. The pooled baseline for the meta-analysis was [redacted] The baseline HbA_{1c} for UK studies in the meta-analysis was higher at 8.9–9.4%. The reduction in HbA_{1c} levels was conditional on baseline and could be estimated by a regression equation.

For the 'UK-relevant' analysis a greater decrease of 1.29% in HbA_{1c} levels from baseline – as estimated by the regression equation given the higher baseline HbA_{1c} in the UK population – was used.

A third analysis, the 'conservative UK' analysis, assumed a decrease in HbA_{1c} levels of [redacted], which was the midpoint between the two values in the other analyses. The decrease in HbA_{1c} levels was applied to a baseline of 9.4% to reflect uncertainty surrounding the actual effect of CSII on HbA_{1c} levels. The rate ratio for severe hypoglycaemic episodes during treatment with MDI compared with CSII was [redacted], with the baseline rate of [redacted] episodes per 100 patient years. Health state utilities were those reported from the UKPDS, which was conducted in people with T2DM.

Results

All three scenarios showed a gain in QALYs for people receiving CSII compared with MDI at an increased cost. The ICER for CSII compared with MDI was £34,330 per QALY gained in the 'trial-based' analysis, £16,882 per QALY gained in the 'UK-relevant' analysis and £22,897 per QALY gained in the 'conservative' analysis. The assumptions for the analyses and resulting cost-effectiveness estimates are shown in table 2. The cumulative incidence of diabetes-related complications was generally lower for those people receiving CSII, except for angina, congestive heart failure, cataract and stroke; this was likely to be a result of the modelled improved patient survival in the CSII arm. Univariate sensitivity analysis showed the results were sensitive to the time horizon and the treatment-associated change in HbA_{1c}.

Table 2 Results of manufacturers' cost-effectiveness analyses

	Baseline HbA_{1c} levels in the MDI group	Decrease in HbA_{1c} levels in the CSII group	Severe hypoglycaemia rate in the MDI group	Severe hypoglycaemia rate in the CSII group	ICER (£)
Trial-based analysis	9.4%	[redacted]	[redacted]	[redacted]	34,330
UK-relevant analysis	9.4%	1.29%	[redacted]	[redacted]	16,882
Conservative UK analysis	9.4%	[redacted]	[redacted]	[redacted]	22,897
CSII, continuous subcutaneous insulin infusion; HbA_{1c}, haemoglobin A_{1c}; ICER, incremental cost-effectiveness ratio; MDI, multiple-dose insulin.					

The Assessment Group commented that the baseline HbA_{1c} levels, as well as the improvements with CSII used in the manufacturers' submission, had large standard deviations in the meta-analysis. Although distributions were placed on these parameters in the model, the uncertainty as to effectiveness was not linked to the baseline level. The model did not specify the positive covariance between the parameters that was noted in the meta-analysis. The manufacturers' submission also assumed that the cost of a severe hypoglycaemic episode was £413, which included a hospital stay. However, in clinical practice only a minority of people with severe hypoglycaemia are

actually admitted. The Assessment Group suggested that the cost should be £62, as used in NICE TA 53 (glargine). The manufacturers also left hypoglycaemia-related deaths at the model default, which is zero. The Assessment Group felt this to be an underestimate, with figures in the literature suggesting that in general 2–4% of deaths of people with T1DM are due to hypoglycaemia. The Assessment Group also noted that the submission did not attach any utility value to the fear of hypoglycaemia. In addition, other important outcomes such as the reduction in depression, effect on cognitive impairment in children and non-health-related quality of life gains were not included. The submission also assumed a 25% reduction in the dose of insulin being administered and an associated cost saving. In summary, the Assessment Group felt that the ICERs in the submission somewhat underestimate the cost effectiveness of CSII.

3.2.4 Assessment Group's cost-effectiveness analysis

The benefits of CSII consist of improved glycaemic control measured by a decrease in HbA_{1c} levels, a decrease in the frequency of severe hypoglycaemic episodes, and lifestyle improvements reflected by patient preference and improved quality of life. The major parameter that influences cost effectiveness is the improvement in HbA_{1c} levels because health benefits and complications are modelled through a decrease in HbA_{1c}. The higher the initial HbA_{1c} levels, the greater the subsequent decrease in HbA_{1c}, resulting in greater health benefits and increased cost effectiveness. The other parameter that varied across the cost-effectiveness analyses is the rate of severe hypoglycaemia. Although cost-effectiveness estimates are, in general, not as sensitive to this parameter, hypoglycaemia has been reported to be an important clinical consideration when recommending the use of CSII.

The Assessment Group simulated a cohort of people with T1DM with an average age of 40 years. In the base-case analysis, based on the Insulin Pump Clinical Database, a baseline HbA_{1c} of 8.8% for the MDI arm, and a reduction by 0.9% to 7.9% for the CSII arm, was assumed. Sensitivity analysis for the effect of CSII therapy on HbA_{1c} levels was undertaken using the lower

value of [redacted] from the manufacturers' meta-analysis (lesser effect on glycaemic control) and using a reduction of 1.4% from a baseline of 9.0% (greater effect up glycaemic control). Lastly, the Assessment Group modelled a cohort of people who were assumed to have good control with an HbA_{1c} level of 7.5% (in whom further reductions would not occur) but a high rate of severe hypoglycaemia (134 episodes per 100 patient years), with reductions of 50% and 75% due to CSII treatment (high severe hypoglycaemia rate but good HbA_{1c}).

In common with TA 53 (glargine), a baseline rate for severe hypoglycaemic events of 18.7 per 100 patient years was assumed for the base case. Treatment with CSII was assumed to reduce this by 50% and 75%. Sensitivity analysis also assumed a higher rate of hypoglycaemia of [redacted] episodes per 100 patient years (higher severe hypoglycaemia rates), with reductions of 50% and 75%. The time horizon of the model was also shortened to explore the effect of limiting the model's tendency to overestimate death due to macrovascular complications. A cohort with a younger age was also modelled.

The costs of the pumps were annualised and it was assumed that the associated infusion equipment was changed every 3 days as recommended. For CSII, the daily requirement of insulin was 0.6 IU per kg – less than the 0.7 IU per kg required for MDI. The saving on insulin costs partially offset the higher costs for CSII. CSII was assumed to incur a one-off training cost of £240 when a person starts to use the pump. Both CSII and MDI were assumed to incur the same costs for blood glucose testing.

Quality of life values for the Assessment Group's analyses came from the same source as the manufacturers' submission – from people with T2DM in the UKPDS. The Assessment Group was concerned that the benefits of CSII, such as greater flexibility of lifestyle, improved participation in social activities or decrease in parental stress, would often not be captured in quality of life scores. However, these benefits would be reflected in patient preference. The Assessment Group carried out a systematic review to identify studies of patient preference and quality of life and identified 17 publications (and four

abstracts). Seven of the papers were from RCTs, all but two of which were on T1DM. One was a controlled study and eight were before and after studies in T1DM. A further study comprised a survey covering 2702 people, 97% of whom had T1DM. Any significant differences that were reported for quality of life outcomes favoured treatment with CSII, regardless of the instrument used to measure quality of life. In addition, when asked, people said they preferred CSII, or they opted to continue treatment with CSII at the end of the trial.

Results

The base-case analysis with a reduction of HbA_{1c} levels of 0.9% and a severe hypoglycaemic event rate of 18.7 episodes per 100 patient years reduced by 50%, over a time horizon of 50 years, produced an ICER of £37,712 per QALY gained for CSII compared with MDI. Given the low baseline rate of severe hypoglycaemia rates, reducing these by 0% or 75% did not change the ICER significantly. When a higher baseline severe hypoglycaemia rate of [redacted] episodes per 100 patient years and a 50% reduction was assumed, and baseline HbA_{1c} levels were reduced to 7.9% from a baseline of 8.8%, the ICER was £36,587 per QALY gained. The insensitivity of the ICERs to the severe hypoglycaemic event rate results from the CORE model results being principally driven by the effect on glycaemic control and HbA_{1c} levels. Decreasing the time horizon drastically increases the ICER, with a 10-year time horizon resulting in an ICER of £58,013 per QALY gained. Shorter time horizons however do not capture the full benefit of improved glycaemic control as complications develop in the long term and increased life expectancy is not captured. Reducing the age of the cohort from 40 to 30 years resulted in an ICER of £34,136 over a 50-year time horizon.

When the lower reduction in HbA_{1c} levels ([redacted], as in the manufacturers' submission, from a baseline of 9.0%) was modelled, with a 50% reduction in severe hypoglycaemic events, the ICER was £53,788 per QALY gained for CSII compared with MDI. However, if a greater reduction of 1.4% was used, with no effect on severe hypoglycaemic event rates, the ICER was £24,720

per QALY gained. This underlines the fact that the cost-effectiveness outputs of the model are largely determined by the improvement in HbA_{1c} levels.

In the cohort with good glycaemic control, where there was assumed to be no improvement in HbA_{1c} levels, but a decrease in the severe hypoglycaemic event rate of 134 per 100 patient years – the ICER was £273,992 per QALY gained for a 50% reduction and £152,058 per QALY gained for a 75% reduction. Again, this reflects the CORE model results being mainly driven by the effect on glycaemic control and HbA_{1c} levels rather than rates of hypoglycaemic episodes. However, because avoidance of severe hypoglycaemic events leads to quality of life gains by avoiding the disutility of the event itself, and because of the reduced fear of such events, the Assessment Group modified the model to accommodate the utility loss associated with hypoglycaemic events. An assumed annual 0.01 quality of life increment in the CSII arm as a result of reduced fear of future hypoglycaemic events translated to a discounted QALY gain of 0.15 over an anticipated lifespan of 21 years. In the base-case analysis, this improved the ICER to £29,300 per QALY gained. If the assumed quality of life increment is 0.3, the ICER would be £21,000 per QALY gained.

All results are summarised in table 3.

Summary

All cost effectiveness estimates available for this appraisal are derived from the CORE model. The model results are driven by the improvements in glycaemic control and, to a lesser extent, improvement in severe hypoglycaemia rates. The model appears to overestimate incidence of macrovascular complications with this overestimation worsening as the time horizon increases. The improvements in glycaemic control, observed in clinical trials, are also assumed to persist over the entire time.

The ICERs strongly depended on

- the characteristics of the population treated, in terms of baseline HbA1c and rate of severe hypoglycaemia episodes, and
- the assumptions made about the improvement in HbA1c and reductions in the rate of severe hypoglycaemia episodes, by using CSII
- the assumptions made about the effect of the avoidance of the fear of severe hypoglycaemia utility.

Table 3 Summary of cost-effectiveness analyses with results

	Baseline HbA_{1c} in MDI group	Decrease in HbA_{1c} in CSII group	Hypoglycaemia rate in MDI group	Hypoglycaemia rate in CSII group	Time horizon (years)	Age (years)	Fear of hypoglycaemic events [1]	ICER (£)
Base case	8.8%	0.9%	18.7	50% reduction	50	40	-	37,712
Base case	8.8%	0.9%	18.7	No reduction	50	40	-	39,586
Base case	8.8%	0.9%	18.7	75% reduction	50	40	-	36,373
Higher severe hypoglycaemia rates	8.8%	0.9%	[redacted]	50% reduction	50	40	-	36,587
Higher severe hypoglycaemia rates	8.8%	0.9%	[redacted]	No reduction	50	40	-	41,062
Higher severe hypoglycaemia rates	8.8%	0.9%	[redacted]	75% reduction	50	40	-	33,361
Higher severe hypoglycaemia rates	8.8%	0.9%	[redacted]	50% reduction	10	40	-	58,013
Lesser effect glycaemic control	9.0%	[redacted]	[redacted]	50% reduction	50	40	-	53,788

[1] In the technology appraisal of insulin glargine (TA 53) fear of hypoglycaemic events was considered.

Greater effect glycaemic control	9.0%	1.4%	[redacted]	50% reduction	50	40	-	24,720
High rates of severe hypoglycaemia, good HbA_{1c} levels	7.5%	0	134	50% reduction	50	40	-	273,992
High rates of severe hypoglycaemia, good HbA_{1c} levels	7.5%	0	134	75% reduction	50	40	-	152,058
Younger cohort	8.8%	0.9%	[redacted]	50% reduction	50	30	-	34,136

Fear of hypoglycaemic events	8.8%	0.9%	[redacted]	50% reduction	50	40	0.01 annual quality of life increment	29,300
Fear of hypoglycaemic events	8.8%	0.9%	[redacted]	50% reduction	50	40	0.03 annual quality of life increment	21,000
CSII, continuous subcutaneous insulin infusion; HbA_{1c}, haemoglobin A_{1c}; ICER, incremental cost-effectiveness ratio; MDI, multiple-dose insulin.								

4 Issues for consideration

- What magnitude of improvement in HbA1c (depending on baseline HbA1c), can be assumed with CSII for UK patients, or the subgroup of UK patients, in whom CSII would be cost effective?
- What decrease in the incidence of severe hypoglycaemia can be assumed with CSII for UK patients, or the subgroup of patients in whom CSII would be cost effective?
- What, if any, is the appropriate quality of life weight to attach to the avoidance of the fear of severe hypoglycaemia?
- Given that CORE does not model the paediatric population– how can the results be extrapolated to this population?
- Can any recommendations be made for pregnant women with diabetes?
- Can any recommendations be made for people with T2DM ?
- Is the previous definition of 'failure of MDI' still appropriate? ["impossible to maintain HbA1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self care of their diabetes"]
- What other criteria, in terms of commitment and competence, specialist support and training, need to be specified for people to be eligible for CSII?
- Are their any other subgroups for which CSII can be recommended?

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by The Aberdeen HTA group.

- Cummins E, Royle P, Snaith A et al., Clinical and cost-effectiveness of continuous subcutaneous infusion for diabetes: updating review, August 2007

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope and the assessment report. Organisations listed in I and II were also invited to make written submissions.

I Manufacturers/sponsors:

- Animas Corporation/Johnson & Johnson Medical Ltd (Animas Corporation R1000 Series)
- Medtronic Ltd (MiniMed)
- Roche Diagnostics Ltd (Accu-Check Spirit, Accu-Chek D-TRONplus)
- Smiths Medical International (Deltec Cozmo)
- Starbridge Systems Ltd (Starlet)

II Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- British Dietetic Association
- County Durham PCT
- Department of Health
- Diabetes UK
- INPUT
- Insulin Dependent Diabetes Trust
- Insulin Pumpers UK
- Juvenile Diabetes Research Foundation
- Kensington and Chelsea PCT
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Physicians
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Aberdeen Health Technology Assessment Group
- Association of British Health-Care Industries (ABHI)
- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Diabetes Research & Wellness Foundation
- Eli Lilly & Co Ltd
- National Collaborating Centre for Chronic Conditions
- National Collaborating Centre for Women's and Children's Health
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Novo Nordisk Ltd
- Pfizer Ltd
- The Dose Adjustment for Normal Eating (DAFNE) Steering Group

C Additional references used:

Palmer AJ, Roze S, Valentine WJ et al. (2004) The CORE diabetes model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Current Medical Research and Opinion 20: (Suppl. 1) s5–s26.

Department of Health. Insulin pumps services – report of the insulin pumps working group. March, 2007.